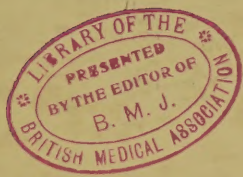


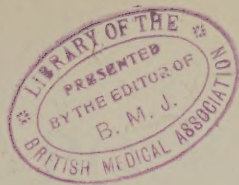
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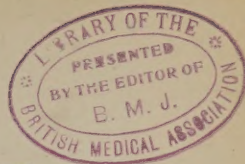


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A TEXT-BOOK OF PATHOLOGY

FOR THE USE OF STUDENTS
AND PRACTITIONERS OF
MEDICINE AND SURGERY

EDITED BY

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A TEXT-BOOK OF PATHOLOGY

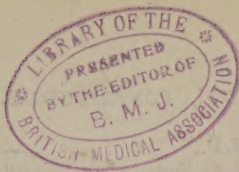
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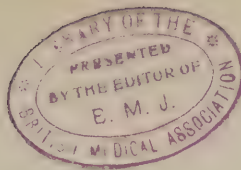
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PREFACE.

THE present volume is the outcome of a desire on the part of the editors and the publishers to place in the hands of the medical student and the physician a comprehensive text-book upon the essential principles and facts in General Pathology and Pathologic Anatomy. Pathology has made such enormous strides in recent years that it is almost an impossibility for one man to make himself fully conversant with the entire field of knowledge in this important branch of science. Realizing this, the editors have endeavored to secure for each of the major departments the services of one who is thoroughly familiar with the particular subject, and can best put the theories and conclusions in an authoritative form. Each writer has been left a large share of freedom in utilizing the material at his hand, so as not to dwarf all individuality—a feature which the editors trust will commend itself to the reader. In this fact lies the explanation why, for instance, references to the literature are more frequent in some articles than in others.

The editors wish to thank heartily all the collaborators in the preparation of this book for their earnest efforts to make the work thorough and useful, and a worthy exponent of the great subject with which it deals. To Dr. John Guitéras, who, previous to his removal to Havana, had taken an editorial interest in the book, the editors are indebted for the privilege of using a number of excellent illustrations. They also desire to express their sincere appreciation of the valuable assistance and patient cooperation of the publishers.



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GENERAL PATHOLOGY.

INTRODUCTION.

HEALTH AND DISEASE.

THE human body consists of cells and of intercellular substances derived from the cells. In the different parts of the body cells of very different appearance and function are met with; thus we speak of epithelial cells, nerve-cells, muscle-cells, bone-cells, cartilage-cells, blood-cells, connective-tissue cells. Portions of the body made up chiefly of one variety of cells constitute a *tissue*; the epidermis is an epithelial tissue, as is also the lining of the alimentary tract; the skeleton consists in part of bony tissue, in part of cartilaginous tissue; the heart is made up chiefly of muscular tissue; the skull is filled mainly with nerve-tissue. Tissues of various sorts are combined in different ways to form *organs*; the liver is made up of epithelial tissue, combined with connective tissue, vascular tissue, muscular tissue, and nerve-tissue; the intestine is composed of epithelial tissue, connective tissue, blood- and lymph-vessels, muscular tissue, and nerve-tissue. All the cells composing the various organs and their constituent tissues have been derived from a single cell—the fertilized egg-cell. Formed by the fusion of a single spermatozoon with a single ovum, this fertilized egg-cell represents the sum of the substances and forces derived primarily from the two parents; that is to say, it is the substratum of the phenomena which we include under the term *heredity*. The fertilized egg-cell lodged upon a normal uterine mucous membrane and finding there conditions favorable to its development, begins to undergo subdivision first into two cells, then into four, eight, sixteen, and later into an enormous number of cells. In its development the fertilized egg-cell—in this case the human organism—is greatly dependent upon and markedly influenced by substances and forces from without it. Not only is this true while the organism remains within the uterine cavity of the mother, but also after it has reached the world outside of the mother. The influences which affect the organism from without are designated *influences of environment*. As far as can at present be seen, the structure and functions of every human organism have to be regarded as the exact resultant of the interplay of inherited substances and forces with the substances and forces in the environment of the organism.

In all probability no two human beings are exactly alike, for in the first place all evidence is in favor of the view that the individual spermatozoa of a given male as well as the individual ova of a given female differ materially from one another; and in the second place, the influences of environment, though sometimes nearly, are never exactly equivalent for two individuals. It is surprising, not that human beings are so different from one another as they are, but rather that they resemble one another in structure and function so closely as we find that they do.

If it be true that all individuals differ more or less from one another, the

difficulties of arriving at a decision as to what is to be regarded as the *normal* individual becomes obvious. The questions "What is health?" and "What is disease?" have been frequently asked, and, it must be confessed, without receiving wholly satisfactory answers. When we begin to form abstract conceptions of an ideal human being we always arrive at mental pictures inconsonant with reality, because demanding conditions of heredity and environmental influence at present unattainable. In medicine, however, we have to deal with real human beings, not ideal ones; and accordingly medical writers have agreed to take the *average* of a large series of observations of structure and function made on human beings who by common consent are regarded as healthy individuals as a standard of the normal, and to regard as abnormal only those deviations from that standard which exceed a certain limit. Thus far the data for the construction of the normal standard of the whole body are insufficient, for to have these it is necessary that the normal standard for all the various organs be determined. The way has been indicated by Thoma.¹ As an example, his study of the weight of the two kidneys in healthy individuals of thirty-five years of age may be instanced. In 200 observations the weight was found to vary between 121 and 491 grams; the arithmetic mean of all the observations was 306 grams. According to the theory of probabilities, 306 grams may therefore be regarded as the most probable weight of the kidneys of a healthy individual thirty-five years old. Of the individual deviations from this weight, half of the 200 observations were contained within the limits 269 (306-37) grams and 343 (306+37) grams. Accordingly, in half of the cases the individual deviations in weight do not amount to more than 37 grams, which may therefore be regarded as the probable standard of individual deviation for the weight of the healthy kidneys at thirty-five years of age. If a normal standard were established for all the structural and functional relations of the body, a normal for the whole body could be set up. Very marked deviations from this normal, exceeding individual anatomic and physiologic deviations in conditions of health, would have to be regarded as morbid or pathologic, and we could then empirically define disease, as Thoma suggests, as a deviation from the normal in the anatomic or chemical structure, or in the functions of the body, its organs and elements of organs, which exceeds the limits of individual physiologic variation. But, as the author of the suggestion admits, such a definition gives no explanation of the nature of disease; it does no more than give the criteria for deciding when any condition is to be called pathologic. Of the many attempts to define disease more fully, none is wholly satisfactory. Chomel's definition is very frequently cited: "Disease is a notable disorder affecting either the material disposition of the constituent parts of the living body or the exercise of their functions," as is also that of Monneret, "Disease is an abnormal state of the living body, characterized by an alteration of structure or by a disturbance of function."

Since the idea of a peculiar "vital force" has been superseded by the conception of "specific cellular activities," the conception has been gaining ground that no hard and fast line can be drawn between normal and pathologic processes. The activities of cells are subject to certain definite laws, which hold in diseased conditions of the body as well as in health. When

¹ Thoma, R., *Untersuchungen ueber die Grösse und das Gewicht der anatomischen Bestandtheile des menschlichen Körpers im gesunden und kranken Zustande*, Leipzig, 1882.

the structure or function of an organism differs markedly from a normal standard for the species, the reason lies either in the abnormality of the inherent activities of some or all of the cells of the organism, or in the abnormal nature of the environmental influences to which some or all of the cells are exposed, or in both. In any of these cases morbid instead of normal reactions are encountered. In the first instance environmental influences, normal for healthy individuals, would call forth morbid reactions; in the second instance individuals previously healthy would become diseased through environmental influences which are incompatible with the maintenance of health because outside the ordinary deviations from the average; and in the third instance the two conditions would be combined.

PATHOLOGY AND ITS SUBDIVISIONS.

The science which studies diseased or abnormal conditions is called *pathology* (πάθος, disease; λόγος, an account of). So extensive a field is included in this term that the science is conveniently divided into several departments. In the first place, it is customary to distinguish General Pathology from Special, or Descriptive, Pathology. By the latter is understood the science which deals with the abnormal conditions in individual diseases; it analyzes the cause or causes of each individual disease, the mode in which the cause leads to morbid reactions on the part of the cells, the structural and functional alterations which are ascertainable, and the course and termination of the disease. It is by no means confined to a study of the postmortem lesions to be found in cases of disease; on the contrary, it deals especially with the phenomena observable during life.

Special pathology is commonly subdivided into *medical*, or *internal*, *pathology*, and *surgical*, or *external*, *pathology*, the former dealing with the deeper and more concealed organs, the latter with those easily accessible. But the domains of medicine and surgery are more and more overlapping one another, so that no strict line can be drawn between the two, and the arbitrary subdivision is simply a matter of convenience. The same is true of the finer subdivisions of special pathology—dermatology, ophthalmology, rhinology, laryngology, gynecology, and the like.

General pathology stands in the same relation to special pathology that philosophy occupies as regards the individual sciences; it is the synthesis of the analyses which special pathology affords. It strives to find out the laws which govern disease in general, searches for the causes of disease, discovers the order of events in diseased conditions, and groups the symptoms and lesions common to whole series of special pathologic processes. It has less to do with the collection of individual facts and observations than with their arrangement and explanation.

Pathologic anatomy deals with the structural alterations or *lesions* observable in diseased conditions of the organism, not only with those which can be made out with the naked eye (*gross morbid anatomy*), but also those ascertainable with the aid of the microscope (*minute morbid anatomy* or *pathologic histology*).

Pathologic physiology studies the deviations of the functions of the organism from the normal under pathologic conditions; in other words, it investigates "morbid reactions."

Pathologic chemistry and physics have to deal with the devia-

tions in the constitution of the substances of which the body is composed and in the nature and disposition of the forces at work in the organism when it is diseased.

That part of pathology which has to do with the causes of disease is known as *etiology* (*αἰτία*, cause; *λόγος*, an account of). The province of *pathogeny* or *pathogenesis* (*πάθος*, disease; *γένεσις*, generation) is to trace the sequence of events from the beginning of the action of the causative agent to the period when the disease has reached its full development.

Human pathology is concerned with the study of diseased human beings only, while *comparative pathology* investigates the processes of disease in animals other than human beings. *Experimental pathology* attempts to throw light upon the phenomena of disease by producing purposely alterations in structure and function under rigidly prescribed conditions.

HEREDITY AND DISEASE.

The mysteries of heredity have occupied the attention of the best minds from the earliest times to the present day, but we are almost as far from any adequate solution of them now as were the philosophers in the days of Lucretius. As concerns the process of fertilization, we have, it is true, gained much information that is interesting. There is good reason to believe that all higher organisms (including man) begin by the fusion of one male cell—the spermatozoon—with one female cell—the ovum. The single cell resulting from the fusion—the fertilized egg-cell—by multiple mitotic division gives rise ultimately to the billions of cells of which the fully developed organism is composed. Spermatozoa and ova are peculiar cells as regards the amount of chromatin which their nuclei contain. By the process of reduction-division (giving off of polar bodies) each ripe ovum comes to contain only half the number of chromosomes present in an ordinary cell of the body of the species concerned; in a somewhat different manner the testicular cells which give rise to the spermatozoa undergo a reduction-division by means of which each ripe spermatozoon contains within it also exactly half the number of chromosomes existent in the ordinary cells of the animal. When the male and female elements fuse, the resulting cell contains a number of chromosomes equal to that of the ordinary cells of the body. The centrosomes of the sperm-cell and the egg-cell fuse, and cell-division of the fertilized ovum begins, the mitosis being inaugurated by division of the newly formed centrosome, with assumption of polar position by the products of its subdivision. In each cell-division the chromosomes undergo longitudinal splitting, each into two hemichromosomes, each of which goes to form a chromosome of the daughter-cells; in this way each of the cells of the body appears of necessity to receive an equal share of the original maternal and paternal chromatin. There is a general belief, based on considerable evidence, that the function of the centrosomes is to determine the multiplication of the cells, while the function of the chromatin (composed of chromosomes) has to do with the production of form and the regulating of the activities of the parts, as, for example, in the differentiation into tissues and organs; to the protoplasm proper of the fertilized egg-cell is attributed the nutritive function, the capacity to attract and transform food-substances upon which depend the life and continued activity of the chromosomes and centrosomes. Interesting as is this belief,

it possesses no value at present other than that of an heuristic working hypothesis.

A description of the process of fertilization is no explanation of the essential nature of the phenomena of inheritance, nor does any one of the various theories which have been advanced—Spencer's doctrine of physiologic units, Darwin's theory of pangenesis, Haeckel's hypothesis of plastidules, or Weismann's germ-plasm theory—help us to any considerable extent toward an understanding of these phenomena. An enormous number of individual facts of the highest interest have been collected, but the generalization which will stand the test of all these is as yet lacking.

The question, Can the characters acquired during the lifetime of an individual be transmitted by that individual to his or her offspring? is one which is much disputed; there are able and enthusiastic supporters on both the positive and the negative side; it is safer for the student, at least in his earlier studies, to regard the question as still open. Pathologists, as a rule, have been forced by their observations to accept, as did Darwin and Lamarck, the positive view; while the majority, perhaps, of biologists have sided with Weismann in denying the possibility of the inheritance of acquired characters. It must be granted that much of what at first thought seems to be most striking evidence in favor of one of the views admits of ingenious explanation on the basis of the other theory.

In a discussion of hereditary disease a sharp distinction must be drawn between disease which is the result of abnormality of the fertilized egg-cell itself and disease which is the result of abnormalities in the environment of the egg-cell from the time of its fertilization up to the birth of the child. The latter should not be considered as inherited disease, but rather as environmental. The human organism begins with the fertilized egg-cell, and birth is only an incident in the life of that organism; in the sense in which we are considering it birth means only a change in environment—from a liquid medium of nearly constant temperature to a gaseous medium of variable temperature, and from a vascular food- and oxygen-supply to a condition in which for food and oxygen the digestive and respiratory apparatus of the organism are called upon to act. It is difficult to determine whether in a given instance a diseased condition is due to an inherited morbid state or to pathologic antenatal environment; but in any event it is helpful to have the distinction between the two sharply in mind.

So-called "variations" are particularly prone to be inherited, and in as far as these are marked deviations from the average they have to be looked upon as examples of pathologic inheritance.

One of the most interesting of the problems for physicians is that of the inheritance of infectious disease. That children are born sometimes with tuberculous, syphilitic, or streptococcic infection there can be no doubt; a large number of cases are on record; and as for tuberculosis, in the tissues of a certain number of newborn infants the tubercle-bacillus has been demonstrated either microscopically or by inoculation of susceptible animals. Certainly, the majority of those cases of infection met with in the newborn are not instances of *germinal infection* (or infection *ab ovo*), but are rather examples of *postgerminal antenatal infection*, the developing organism being infected by contagion from the mother. For in the first place it is doubtful whether a spermatozoon or an ovum containing tubercle-bacilli or streptococci would be capable of playing a successful part in the fertilization

process, and in the second place in a number of the instances encountered uterine or placental disease of the mother has been demonstrated. That germinal infection can occur in animals has been proved in at least one instance—that of *pébrine*, the disease from which silkworms suffer. Without going into the evidence, it may be said that it seems most probable that congenital syphilis is, in some instances at least, a matter of germinal infection in human beings; though doubtless many or most of the cases of congenital syphilis are to be regarded as examples of postgerminal antenatal infection as a result of intra-uterine contagion. The evidence—observation as well as experimental—available at the time of writing is all against the view that tuberculosis or pyogenic infections are ever germinal in origin.

Hemophilia, the condition which exists in the families of “bleeders,” appears to be a disease which more than any other supports the doctrine that pathologic conditions can be inherited. There are on record very complete genealogic trees which prove that hemophilia is transmitted for many generations. Males are much more frequently affected than females; but females who are not bleeders, but who have had bleeding ancestors, may transmit the disease to their male offspring. So little is known of the exact nature of the disease that it is not possible to decide at present whether it represents a “variation” or an “acquired” morbid condition which becomes hereditary.

Diabetes insipidus is another disease which may affect several generations in succession. Males and females appear to be about equally affected.

Deaf-mutism presents interesting features from the view-point of heredity. Congenital deaf-mutism has to be distinguished from deaf-mutism resulting from disease in infancy. Marriages between deaf-mutes result in a high percentage of deaf-mute offspring, but marriages between deaf-mutes and hearing persons result in a still higher percentage of deaf-mute offspring. The explanation appears to be that of the marriages of deaf-mutes with one another, many of the participants are not hereditary deaf-mutes, while in marriages of deaf-mutes with hearing persons the latter are most frequently drawn from families in which hereditary deaf-mutism occurs, and, though not deaf-mutes themselves, possess germ-cells which transmit the affection.

Certain vices of metabolism, such as gout and chronic rheumatism, undoubtedly run in families, and are classed as hereditary diseases. The external manifestations of a gouty condition may vary considerably, even in the offspring of the same individual; thus, while one of the children may, like his father, develop typical gouty joint-affections (*homeomorphous inheritance*), another may be an asthmatic, and still another, perhaps, a sufferer from migraine (*heteromorphous inheritance*). Among the most striking examples of this dissimilar, or so-called heteromorphous, inheritance are those met with in the domain of neuropathology. It is far less common to find children inheriting the same disease as that occurring in one or both of their ancestors than to meet with those who suffer from some nervous disease other than that by which their ancestors were attacked. By many it is believed that only a “neuropathic predisposition” is inherited, and that the character of the nervous disease which develops is dependent upon the particular form which this predisposition takes, together with the special noxæ to which the individual during his lifetime is exposed or from which he is protected. A remarkable attempt to illustrate such heteromorphous heredity

in fiction has been made by Emile Zola in his series of novels dealing with the Rougon-Macquart family.

The so-called homeomorphous heredity is well illustrated by the "family diseases" of the nervous system, such as Friedreich's ataxia, and some forms of insanity.

An hereditary tendency to the formation of neoplasms has been emphasized by many authors; the view agrees well with the theory of the origin of tumors advanced by Cohnheim, but a careful analysis of available statistics does not warrant the conclusion that new growths are inherited.

Ehrlich's experiments with abrin, ricin, and other poisons indicate that immunity from intoxication can be transmitted from mother to offspring, and observations on some of the infectious diseases make it probable that a temporary and probably passive immunity can be given to the offspring in such cases by the mother. There is no evidence that an immune father can confer immunity upon his descendants. It seems likely, therefore, that the immunity given by the mother is not a germinal immunity, but a chemical and passive immunity yielded through the maternal blood-supply. In other words, we have at present no evidence of direct inheritance of acquired immunity, but rather some instances of temporary immunity conferred by postgerminal antenatal environment. It is different with natural immunity. This is undoubtedly a matter of inheritance, but in all probability not an example of inheritance of acquired immunity. It would seem much more likely that through natural selection the specially insusceptible had survived, the susceptible sometimes dying from the disease and yielding a less numerous posterity, gradually becoming eliminated.

Some infectious diseases of the parents, instead of making the offspring less susceptible than other individuals, have the opposite effect. This is pre-eminently true of tuberculosis; but just how tuberculosis of the parent gives rise in the offspring to an *hereditary predisposition* to tuberculous infection remains for the present obscure.

That the future has much in store for us in the clearing up of the problems of pathologic inheritance no one can doubt. A valuable clue and a basis for experimentation lie in the important fact that the ovaries and testicles are nourished by the blood of the general circulation. That the nutrition of these organs must vary with alterations in the general nutrition of the body seems obvious; that the cells of these organs can escape the ill effects arising from the action of poisons in solution in the general circulating blood would seem impossible. In thus far, at any rate, the acts of the parents cannot fail to influence their offspring either for good or ill, and the advice of Jean Lahor, in his *Benediction of the Persian Marriage*, aptly cited by Le Gendre, cannot be too often repeated:

"Pour que vos actions ne soient vaines ni folles,
Craignez déjà les yeux futures de vos enfants."

ENVIRONMENT AND DISEASE.

Living organisms, multicellular as well as unicellular, at all stages of their existence are exposed to influences acting upon them from without. Indeed, in the absence of these influences life is scarcely conceivable, for the phenomena of life with which we are familiar appear to consist exclusively of a continuous adjustment of internal to external relations. There is no

evidence whatever of spontaneity of action in any living organism ; on the contrary, all known facts favor the view that every manifestation of energy on the part of an organism is to be looked upon as a reaction to some external influence. The reaction to external agents is not always immediate, however ; the cells of the body have the capacity of storing up stimuli, as it were, until through a process of summation some final stimulus leads to a discharge. This accounts for the fact that a vital reaction often appears to be out of all proportion to the external influence immediately occasioning it, when in reality this influence is only the last of a series of stimuli which at various times during the life of the organism have acted upon the cell or group of cells representing the physical basis which underlies the reaction. It is in connection with the nervous system especially that such retarded reactions are very commonly noticed.

The environment to which every human being is exposed varies enormously at different periods of life ; the most abrupt change is that which occurs at his birth, but throughout later life there are continual slight alterations, and, with the majority of individuals, frequently changes of a very decided character. With a given inheritance, the individual which results can vary only according to the environmental influences which act upon the organism from its beginning as a fertilized ovum to its death.

It is convenient to divide environmental influences chronologically into (1) those which act before birth and (2) those which affect the individual after his birth ; or, briefly, into *antenatal* and *postnatal* environment.

Although the period of antenatal environment is very short as compared with the average duration of postnatal influences, it is of the very highest importance as regards the future welfare of the organism concerned. This antenatal period is arbitrarily divisible into an *embryonal period* and a *fetal period* ; the former corresponds in human beings to about the first two months of gestation, the latter to the remainder of intra-uterine existence. During the embryonal period the fertilized egg-cell rapidly divides, differentiation of cells takes place, and the organs of the body are formed ; during the fetal period the organs thus formed increase in size and begin to take on their characteristic functions. In both stages of this antenatal period the organism is dependent upon influences outside itself—on gravity, warmth, an adequate amount of food-supply of the right sort, etc. Considerable deviations from a certain normal standard of these external influences can and do lead to pathologic conditions in the developing organism. In the embryonal period especially abnormal environmental relations may lead to the most serious results ; for since this is the time when the various organs are being formed, there may be arrest of development, excess of development of certain parts, or a perversion of the organ-formation ; accordingly, this is the period when the fate of the form of the organism is decided, whether the normal form of the species will be attained or whether a malformation or a monster will result. The experimental teratologists have furnished us with valuable data as to the effects of abnormal environment of various sorts, and monsters of different kinds can be produced by submitting the fertilized egg-cell, the segmentation-cells, or the blastoderm to the effects of light, cold, heat, variations in oxygen-supply, and especially certain chemical agents. That morbid form-relations in the organism can be dependent upon abnormal environment in the embryonal period may, therefore, be considered as proved, and pathologists are busy studying the

various abnormalities which may occur in human beings as a result of injury at this time, and are endeavoring—though as yet with but little success—to determine the exact relations which exist between a given alteration of the environment and definite anomalies of development. The difficulties of the study are obvious, and are not lessened by the fact that one primary developmental alteration may carry in its train as sequences a whole series of secondary alterations in the embryo.

Though not proved, it is *a priori* extremely probable that poisons acting electively on the embryo at an early period of cell-differentiation can render permanently abnormal one or more cell-systems of the body; it is not impossible that one day an explanation of the low resistance offered by certain of the tissues of some individuals in adult life may here be found.

In the fetal period of antenatal environment the organism is endangered less by the effects of physical agents than by those of a chemical nature. The chemical constitution of the maternal blood is of prime importance at this stage. Infections, and more particularly intoxications, of the mother may be transferred to the child; uterine or placental diseases especially may be of very serious import for the fetus. Children born with tuberculosis, syphilis, or pyogenic infections are nearly all instances of contagion from antenatal environment. At the time of birth itself a narrow pelvis in the mother or the use of forceps by the physician may mechanically injure susceptible parts—especially the head—of the child. Considering all the avenues of danger open, it is surprising that so many children are born healthy; it is fortunate, too, that, thanks to the seething energy of the developing cells, the reparative and adaptive powers are at a maximum in these early stages of life.

Postnatal environment beginning at birth continues throughout the remainder of the life of the individual. The external influences which can act upon man are, in the last analysis, either chemical or physical; the medium in which he lives, the air he breathes, the food-stuffs taken, the temperature of his surroundings, gravity, light, electricity, and ether-waves are among the things to be considered. The external agencies which act through the sense-organs—the ether-waves that affect the rods and cones of the retina, the air-waves that set in motion the vibratory apparatus of the ears, the chemical substances which act upon the olfactory and gustatory mucous membranes, the mechanic and physical agents which start the impulses in cutaneous sensation—belong to the same category. In conscious life memories are called forth and association processes are started into activity by stimulation of one or more of the sense-organs by these physical or chemical environmental influences; even the influence of one mind upon another is possible, as far as we know, only through the sense-organs of the one influenced.

With a given inheritance the best development of the capacities of an organism doubtless requires a specific environment varying constantly according to the needs of infancy, adolescence, and the stages of adult life. But our knowledge of the relations of specific environments to definite inheritances is so extremely limited that few would be rash enough to have much faith in their prescriptions in a given case. Moreover, aside from the impossibility of knowing what a given inheritance is, there is seldom opportunity for more than meager alteration of environment by prescription; in most particulars this is predetermined, a given human organism living of

necessity in a particular region with its geologic formation and meteorologic influences, subject to the racial conditions in which he is born, surrounded by the conditions pertaining to the social level in which he happens to be placed and to the special modifications of these which the occupation of his parents and his own, in the general division of labor, necessarily entails. Of the vast number of potential capacities inherent in each developing individual, the one which shall be especially developed at the expense of the others is decided by certain exigencies in environmental relation—sometimes by such as we are accustomed to designate as “merely accidental.” The result is, therefore, that the environment which comes to a given inheritance is very far removed from that which an all-seeing intelligence would prescribe as that specifically ideal for the individual. No individual finds a perfect environment; but the degree of dissonance varies enormously in different cases, and though the wonderful adaptive powers of an organism permit it in many instances to attain to a comfortable and profitable state of existence, in an appalling number of cases the lack of harmony is so great that a high degree of discomfort and inefficiency, disease, or premature death is the outcome. It may be true that for the good of the species, or for the welfare of living organisms as a whole, such a state of things is desirable; indeed, this is in large part the basis of the doctrine of evolution, with its tenets of “natural selection” and “survival of the fittest.” A favorable environment in any case is not one free from struggle, but rather one in which the organism is victorious in its conflicts and in which the victory is not bought at too great a price.

All pathologists are now agreed that by far the majority of pathologic conditions are the result of external causes; *i. e.*, are due to inimical environmental influences. These are divisible into (1) *efficient causes* and (2) *predisposing and accessory causes* of disease.

The *efficient causes* of disease (*causæ proximæ sive determinantes*) are the immediate or direct causes. Thus, the cholera-spirillum is the efficient cause of cholera, the *Micrococcus lanceolatus* is the efficient cause of acute lobar pneumonia, the heat of the sun's rays of insolation, lead-poisoning of wrist-drop.

The *predisposing and accessory causes* of disease (*causæ prædisponentes sive remote*) include those which render the body more susceptible to the efficient cause. Thus, external agents which render the contents of the stomach alkaline are believed to predispose to infection with the comma-bacillus of cholera; exposure to cold and wet predisposes to acute lobar pneumonia; alcoholism predisposes to insolation; and certain occupations make lead-poisoning possible, and in a sense may therefore be regarded as remote causes of lead-paralysis. That an efficient cause of one disease may be a predisposing cause of another disease, and *vice versa*, is obvious.

In the special sections of this work the various diseases together with their immediate and remote causes will be discussed. The influence of mechanic injury, of physical agents—heat and cold, light, electricity, x-rays—and especially of chemical agents, including the various poisons, will be considered; especial attention will be paid to bacterial infections and invasions by animal parasites, conditions in which poisoning is the chief factor, as a rule, though mechanic injury plays sometimes also a part; reference will be made in some instances to the pathologic reactions called forth by way of the nervous system, a most important field for study,

but one which is as yet only being approached. An attempt will be made also to pass beyond the mere etiology of the various diseases, and, where knowledge warrants it, to enter into a description of the pathogenesis of the different processes, for even more important than to know *why* disease occurs is to know *how* it originates.

HEALING AND CURE.

When the external influences acting upon the cells of the organism are so pronouncedly inimical that certain of those necessary for the continuance of life are so injured as no longer to be capable of performing their functions, death occurs. Until death occurs, or in case it does not occur, the organism attempts to protect itself against injury, to repair the injury done; or, in case the injury is irreparable, to adapt itself as well as possible to the altered conditions under which it has henceforward to live. These efforts constitute what is ordinarily designated as the "healing power of nature" (*vis medicatrix nature*). In general parlance the word *healing* is applied most often when surgical injury is in mind, the word *cure* when internal pathologic processes are thought of; but the distinction is merely arbitrary, and the two words are frequently used indiscriminately. The protective, antidotal, regenerative, compensatory, and adaptive capacities of organisms are among the most interesting subjects with which the pathologist has to deal, and it is chiefly from a study of them that methods of successfully dealing with the natural processes spring. Natural attempts are sometimes excessive and need to be limited; at other times they are defective and require to be supplemented; here lies the province of *therapy*.

In the process of evolution special mechanisms capable of protecting organisms against injury from the external agents ordinarily encountered have been developed; but these, wonderfully intricate and ingenious as many of them are, are frequently insufficient; the organism has then to combat as best it can the effects of the injury. The struggle of the human organism against bacterial infection may be taken as an example. The environment of each individual is such that he comes into contact relation with certain microorganisms which are capable of causing disease in human beings. He is constantly in contact with some of these, only occasionally in contact with others. His protective mechanisms, if in normal condition, protect against the ingress of most of these microorganisms; there are some against whose ingress there seems to be no normal protective mechanism. If from any cause there is a breach in one of the natural barriers, bacteria against which there is normally protection may enter the organism, multiply, and by their toxic products injure the cells of the body. Efforts are made to kill the invading organisms (*phagocytic activity of the cells, bactericidal power of the blood and tissue-juices*), to wall them off (*inflammatory reaction, encapsulation*), to get rid of their toxic products (*increased activity of eliminative organs*), or to neutralize their effects (*development of antitoxins*). If the infection leads to the death of some of the cells, they are replaced by cells of the same kind (*regeneration of tissue*); or if this, owing to the extent of the injury or the nature of the tissue injured, is impossible, by cells and intercellular substances of a different kind (*proliferation of connective tissue or glia, cyst-formation*). Some of the injuries caused to certain organs may never be directly repairable; then often secondary alterations in other and

often distant organs are necessary to reëstablish the vital equilibrium (*compensatory and adaptive processes*). Not infrequently an infection leads to the development in the organism of entirely new mechanisms of defence which protect it from any subsequent infection of the same kind (*acquired immunity*).

It is seldom that what we designate as healing or cure is associated with a complete restoration of the previous condition (*restitutio ad integrum*); indeed, it is likely that every disease-process leaves behind it indelible alterations in some of the cellular constituents of the body. These cellular bequests may be of little or no significance at times; in many cases, however, they are responsible for the development later in life of pathologic processes of a serious nature.

IMMUNITY.

When an organism, subjected to the action of some influence noxious to certain other organisms, is found to be insusceptible to it, that organism is said to be *immune* from that particular noxa. If this immunity has been enjoyed by the organism from its beginning, and has not been due to reactions occurring in it during its lifetime, the immunity is said to be *natural*, *innate*, or *hereditary*. If, on the other hand, the immunity is the result of changes which have taken place in the body during the lifetime of the organism, it is spoken of as *acquired immunity*. Immunity gained during the intra-uterine life of a higher animal may be called *antenatal acquired immunity*, while that developed during its subsequent life may be referred to as *postnatal acquired immunity*. Immunity is usually acquired by an organism after an attack upon it by some external agent, coming to it accidentally in the course of its life. This may well be designated *unintentional immunity*. It can be acquired in a certain number of instances through the direct, purposeful intervention of human agency, in which case we may speak of *intentional* or *artificial immunity*.

Though in the strict sense of the word immunity indicates complete protection, it is not customary so to limit its meaning. Complete insusceptibility is referred to as *absolute immunity*, while lesser degrees of insusceptibility, a certain marked resistance to injury being offered, are spoken of as *relative immunity*.

Natural, Innate, or Hereditary Immunity.—It has been known for ages that certain organisms are naturally susceptible, while others are naturally resistant to given noxæ. Species and races show marked differences in this regard. Many species of animals are seriously poisoned by the venom of the viper, while the hedge-hog is naturally immune therefrom. Man is susceptible to many infectious diseases—*e. g.*, typhoid fever, syphilis—which, as far as we know, never occur in the ordinary course of nature in other species of animals. Again, various infections to which animals are very susceptible may not influence human beings, or only to a limited extent. Different races of men vary much in their susceptibility to poisons and infectious agents. The negro has a relative immunity from the effects of alcohol; he is but seldom attacked by malaria or by yellow fever.

With a given species, natural immunity varies with the age of its constituent individuals. Thus, for example, typhoid fever is rare in human beings in infancy. Children possess a relative immunity from the effects of arsenic, belladonna, and other poisons. It is uncommon to meet with cases of osteomyelitis in adults, while the disease is frequent in the young.

Again, among individuals, even when of the same age, there are remarkable variations in susceptibility to noxæ. Thus, most people can take relatively large doses of quinin without suffering inconvenience; others are cinchonized by small doses of the drug. In epidemics of cholera, small-pox, yellow fever, bubonic plague, etc., there are certain individuals who, never having had a previous attack and in spite of manifold opportunities for contagion, never contract the disease.

Most interesting are the differences in resistance offered by the various organs and tissues of the same individual in cases of intoxication or infection. The pathologist is constantly struck by the relative immunity of certain organs—*e. g.*, in tuberculosis, in typhoid fever, in pyemia.

Acquired Immunity.—The tolerance acquired to poisons by those who begin with small doses and continue their use, gradually increasing the amount taken, is matter of common experience. The alcoholic *habitué*, the morphinist, the Styrian arsenic-eater, will be immediately recalled to mind.

Many infectious diseases yield immunity by a single attack. Scarlet fever, small-pox, typhoid fever, syphilis, seldom affect an individual more than once, and when they do the second attack is always extremely mild. Here we have to deal with postnatal unintentional acquired immunity.

Children born of a mother who has suffered from small-pox during her pregnancy and recovered without miscarriage may be (but are not always) immune from small-pox—an example of antenatal acquired immunity.

The history of artificial acquired immunity begins with the introduction of vaccination by Jenner. With the advent of the bacteriologic era and the establishment of the relation between definite bacteria and specific infectious diseases, Pasteur and his co-workers attempted to produce artificial immunity against bacterial infection. He was able by inoculation of chicken-cholera bacilli whose virulence had been artificially attenuated to protect animals against infection with virus of full strength. It was soon found possible to produce immunity against a whole series of infectious diseases by inoculation of weakened cultures of bacteria or by ingestion of their products. Protection against anthrax, rabies, bubonic plague, and cholera can be afforded to human beings in this way. These immunizing methods were, however, all preventive rather than curative.

A method which will cure an infection already in progress has been found for a certain number of diseases, the most striking example of which is diphtheria. The blood-serum or other fluids of an animal rendered artificially immune from diphtheria, when injected into an animal suffering from the infection, will afford speedy relief. The healing substances in the serum of the immunized animal—so-called antitoxins—can be enormously increased in amount by special methods. Antitoxic serums against diphtheria, tetanus, and snake-poison have been made practically useful; the results in diphtheria are eminently satisfactory, but in tetanus there is still much to be desired. This rapid form of vaccination can also be employed as a prophylactic measure, but it yields only temporary immunity. It has been called *passive* immunity by Ehrlich, to distinguish it from the *active* immunity yielded by an actual attack of the disease or by vaccination with the bacteria or their toxic products.

Theories of Immunity.—A number of theories attempting an explanation of the essential nature of immunity have been advanced. Of those supported at the moment, two main groups may be distinguished:

1. The *humoral theories*, which attribute immunity to the properties of the extracellular fluids of the body (bactericidal, attenuating, antitoxic properties); and 2. The *cellular theories*, which assume that the body is protected through the direct and active intervention of the living cells themselves.

The **humoral theories** are based largely upon the studies of Fodor, Nuttall, Flügge, Behring, and Buchner. They assume that the bacteria are killed through the bactericidal action of the blood-serum itself, or that the poisons produced by the bacteria are rendered inactive, according to Buchner, in that the blood-serum renders the specifically irritable cells of the body insusceptible to the action of the poisons, or according to Behring, in that the blood-serum actually destroys the poison made by the bacteria. The bactericidal power of the blood is attributed by Buchner to the presence in it of certain labile chemical bodies, which he calls *alexins*, and to which Hankin has given the name *defensive proteids*; these bodies are believed by Kossel and by Vaughan to be derived from nuclein or nucleinic acid. Baumgarten questions the presence of specific bactericidal substances in the serum, and believes that its action can be explained on the grounds of plasmolysis. If this be so, it is strange that the bactericidal power should be abolished by heating to a temperature of from 57° to 60° C. That no change in the ionic concentration of the blood-serum demonstrable by the methods of measuring electric conductivity results from this heating, has been proved by Looz and Tallant. Even those who adopt a humoral theory of immunity grant that the bactericidal, attenuating, and antitoxic substances are derived from the cells.

Metschnikoff's **phagocytic theory** of immunity is the chief of the cellular theories. The learned biologist at the Pasteur Institute has during the past sixteen years combated, he believes successfully, every objection which has been raised against his doctrine. Immunity, he asserts, is dependent upon the activity of the living cells. Any bactericidal action of the body-juices is the result of secretions derived from stimulated leukocytes or endothelial cells. Among the cellular elements which take part in immunity, the phagocytes occupy the first rank. The main factors of the activity of the phagocytes are their sensibility and motility, their capacity of taking up solid bodies, their power of forming substances which will kill and digest microbes. If these properties are possessed in such a degree that a given pathogenic microbe cannot develop in its body, an animal is said to be naturally immune against that microbe. If all or one of these capacities should be insufficiently developed, the animal is susceptible. If the microbial products call forth a negative sensibility in the phagocytes (negative chemotaxis), as in the acute septicemias, then the parasites increase, as in a culture-tube, and soon kill the organism. Should the products of the microbes positively influence the phagocytes so that the latter become directed toward the microbes, but are unable to ingest them, the animal cannot live (*e. g.*, anthrax infection of the guinea-pig). In an infection in which the phagocytes are attracted by the microbes and the latter are ingested by the former, if the cells are not able to kill the microbes within their bodies, the course of the infection is slowed more or less, but death ultimately results (*e. g.*, mouse-septicemia, tuberculosis in susceptible animals).

The activity of the phagocytes is, Metschnikoff continues, artificially alterable. Thus fowls, ordinarily immune from anthrax, can be rendered artificially susceptible by exposure to cold. Further, an animal ordinarily

susceptible to a given infection, can through stimulation of the phagocytic activity be rendered artificially immune. If this stimulation be temporary (as in the passive immunity of Ehrlich), then the immunity lasts but a short time; if it be produced by inoculation of the bacteria or their products (as in the active immunity of Ehrlich), it may last for a much longer period.

A full discussion of the subject of immunity cannot be entered into here. It may suffice to say that with this subject, as with so many which are energetically discussed, the truth appears to lie in a mean which harmonizes more or less the two opposing views. Both the cells and the extracellular fluids are concerned in the phenomena of immunity, each probably varying in degree in the different varieties of the process. Immunity is a most complex subject, and a satisfactory explanation for one infectious disease will by no means hold for another.

A word must be said with regard to the **lateral chain theory** (*Seitenkettentheorie*) of Ehrlich. This ingenious experimenter works on the hypothesis that in the protoplasm of the body-cells are contained highly complex organic molecules with a tolerably stable central group, to which are attached far less stable lateral chains of atoms or atomic groups—lateral chains (*Seitenketten*). The ordinary chemical transformations in the protoplasm are carried on by means of these lateral chains, the stable center of the molecule remaining unaffected. Poisons entering the body do injury if they find lateral chains with which they can unite (*receptors*); as lateral chains become united with these poisons the cells are stimulated to form new lateral chains, and, according to a well-known physiologic law of regeneration, will build them in excess. Ehrlich assumes in an animal rendered artificially immune from diphtheria that there is an overproduction of lateral chains by the cells, and it is these excessive lateral chains which, thrown off by the cells into the blood, constitute the antitoxins. These free lateral chains of antitoxic serum can bind and so render neutral the toxins produced by the diphtheria-bacilli, thus preventing their union with the lateral chains of the body-cells themselves. Ehrlich's explanation of immunity in infectious diseases like typhoid fever, cholera, and the like is somewhat similar. Immunity in these cases is antibacterial rather than antitoxic; that is to say, the body-fluids of immune animals destroy the typhoid bacilli and the cholera-bacilli themselves, instead of rendering neutral their poisons. In this form of immunity the lateral chains produced in excess by the body-cells act as the *immunizing body*, but in a peculiar way. In the normal blood-serum are contained substances which possess the power of dissolving bacteria, but these substances cannot act except by the intervention of another chemical substance. This intermediate rôle is played by the immunizing body. Only after the latter has united with the protoplasm of the bacterial cell can the dissolving substance (*addiment*, *end-body*, or *complement* of Ehrlich) unite with it and begin its solvent effect. Ehrlich and Wassermann believe that by regulating the amounts of the *immunizing body* and the *complement* in curative serums it may be possible to make serotherapy practically useful in a group of diseases in which it has hitherto been of no avail.

Immunity can be produced not only against poisons and bacteria, but also against a variety of animal cells, such as spermatozoa and red and white blood-corpuscles. In the production of these immunities a variety of cell-destroying substances (*lysins* of Ehrlich) are formed. These in turn, if introduced into the body of another animal, may give rise to *antilyns*.

Autolysins, homolysins or isolysins, and heterolysins are distinguished according as the lysin produced destroys cells of the animal's own body, those of an animal of the same species, or those of an animal of a different species; but the subject grows too complex to be further followed here.

ADAPTATION IN PATHOLOGIC PROCESSES.

In pathology the term adaptation is employed to designate the morbid processes—compensatory, regenerative, self-regulatory, protective, or healing—which bring about some sort of adjustment to changed conditions due to injury or disease.¹ Adaptive processes in physiology are familiar to all; the maintenance of an almost constant temperature in higher animals notwithstanding marked alterations in the temperature of the environment, and variations in the amount of heat produced in the body itself, and the regulation of the force and frequency of the beat of the heart according to the amount of work it has to do, are striking examples.

Physiologic adaptations must be looked upon as cellular responses to environmental alterations dependent upon innate properties in the cells, which in turn, in large part at least, are dependent upon evolutionary factors. It does not seem likely, however, that variation, natural selection, and heredity can have operated directly so as to endow the cells of an organism with properties which especially fit them to meet pathologic emergencies. On the contrary, the evidence is in favor of the view that all or nearly all adaptations under pathologic conditions have their foundation in physiologic processes or mechanisms (Welch). As examples of adaptation in pathologic processes may be mentioned the cardiac hypertrophy which accompanies chronic renal disease, the compensatory hypertrophy of the heart when there are serious lesions of one or more valves of that organ, the collateral circulation which develops when there is obstruction to the flow of blood through the portal vein, the vicarious emphysema of one part of a lung when another part of it is consolidated, the increase in size of cells and their multiplication in one kidney when the other is diseased or has been removed by the knife of the surgeon, the thickening in the wall of a blood-vessel which occurs when the tension inside that vessel has for a long time been increased, the reorganization of the functional activity of neural complexes when one or more neurone-systems have been thrown out of function. The various pathologic regenerations, and even inflammation and acquired immunity, may also with fairness be included under the head of adaptive processes which follow injury or disease.

The inadequacy of pathologic adaptations contrasts markedly with the perfect compensations afforded by physiologic adjustments. While the purposefulness and benefit of the adaptive changes in many pathologic processes are obvious, their inefficiency and even dangerous consequences are only too frequently observable. The thickening of the vessel-wall in arteriosclerosis has its advantages, but it is far from being a satisfactory adaptive arrangement. The reaction of the body-cells to the syphilitic virus is doubtless protective in nature; but when a gumma presses upon an important convolution in the brain the benefit is more than counterbalanced by the attendant

¹ For a more extensive discussion of this subject, the student should consult the article by W. H. Welch, "Adaptation in Pathologic Processes," Congress of American Physicians, iv., 1897, *Science*, N. S., vol. v., No. 126, pp. 813-832, 1897.

evil. The benefit or harmfulness of the adaptive processes has been much discussed in connection with inflammation. Some view inflammatory processes as almost always inimical to the organism, always to be artificially combated; others regard them as the best protective mechanisms which the organism under certain conditions possesses, mechanisms which are to be controlled and aided artificially rather than combated. One thing we may be sure of, the phenomena of inflammation, like those of all other processes, are the necessary sequence of the interaction of external forces and the forces inherent in the cells themselves.

Given an organism made up of cells with certain innate properties, the response to stimuli from the outside will vary with the external stimulus, but will always be determined by the nature of the substances and forces inherent in the cells. It is the function of the pathologist to discern as best he can the mechanic factors which underlie adaptive responses; in this task he is more likely to be hindered than to be helped by indulgence in teleologic considerations. Were the adaptations in what we call pathologic processes perfect, there would be no need of therapeutic interference; as it is, however, their imperfections stimulate the physician and surgeon to ever-renewed exertions.

ON THE METHODS OF STUDYING PATHOLOGY.

The phenomena of disease are so complex and the problems connected therewith so difficult that it is folly for the untrained mind to approach them. Before entrance upon the study of pathology, therefore, a liberal education is a *sine quâ non*. There is difference of opinion regarding the most desirable extent of this preliminary training, but most will agree that it should go far enough to put the student on a level with the liberally educated men of the professions of law and theology; and that it should not be prolonged to an age when plasticity is endangered, for the student should enter upon the study of pathology while he is still easily impressionable and capable of an ardent enthusiasm.

In his early education the subject-matter of the student's work is probably less important than the manner of it; with whatever his studies may be concerned, the essence of the training should be directed toward the development of his powers of analysis, the cultivation of his imaginative faculties, the strengthening of his capacity for weighing evidence, and, above all, the encouragement of the expressive activities. The mind trained to observe accurately and to think logically, if combined with imaginative powers, will be the one most likely not only to grasp quickly knowledge already existent, but also to add to that knowledge.

Since disease represents a deviation from the normal, it goes without saying that its processes must remain unintelligible to one unacquainted with normal structure and function. Just as physics and chemistry are subjects, the study of which necessarily precedes a successful study of anatomy and physiology, so the study of the latter subjects naturally antedates the study of pathology. Again, comparative anatomy and physiology, along with embryology, have thrown much light upon the structure and function of the normal human organism; they are also very useful in helping to explain many of the phenomena met with in diseased conditions—indeed, we owe no small part of our modern conceptions in pathology to phylo-

genetic and ontogenetic considerations. A study of these subjects, therefore, will naturally be prefatory to a study of pathology.

It is by no means necessary that the student of pathology shall be equally well prepared in all these antecedent studies—biology, physics, chemistry, anatomy, physiology; on the contrary, with a good general knowledge of each he may be the better able to make advances in pathology if he have had a very special training in some one of them—witness the value of Pasteur's knowledge of chemistry, of Helmholtz's command of physics!

To keep pace with the world's activities in the domain of pathology the student has to follow closely the books and periodicals bearing upon the subjects which are constantly appearing. To do so he has at present to read several languages in addition to English. French and German are essential, and Italian is desirable; Spanish and Russian are of less service, though occasionally of advantage.

Diseases or their effects may be studied in man and animals during life or after their death. The studies made during the life of human beings are usually spoken of as *clinical*; those made after death upon human beings and those made both before and after death upon animals are usually carried on in the *laboratory*. No sharp line can, however, be drawn between clinical and laboratory studies; the laboratory is only an extension of the hospital ward, and in a sense the ward may be regarded as a form of laboratory; in both places pathology, the study of disease, is the subject prosecuted.

In the solving of problems in pathology both inductive and deductive methods are employed, for sometimes the latter are applicable when the former offer no satisfactory modes of approach. When investigating pathologic processes in human beings we are limited almost entirely to observational methods; but in animals, fortunately, the results of observation may be supplemented by those of experimental inquiry. All scientific work is based upon the assumption that the course of nature is constant; in other words, that the world of phenomena is reducible to a series of uniformities which are designated ordinarily Laws of Nature. In the study of the phenomena of disease we have to attempt to reduce the more complex uniformities met with to terms of the simpler uniformities of which they are composed. The relations of a given phenomenon to those which coexist with it, to those which have preceded it, and to those which will follow it, have to be determined. Here the powers of *observation* have to be strenuously exerted. At any given moment in the course of a given disease a complex group of phenomena presents itself for examination. This group must be analyzed; the observer strives to make out the individual parts of which the whole complex is composed. All the phenomena observable have to be regarded as consequents of antecedent phenomena. The inquiry has then to be directed toward the antecedent phenomena, and the attempt made to determine which consequents are related to which antecedents; antecedents and consequents are in every instance observed so numerous that in order to establish any relations of cause and effect it is necessary to observe other instances in which some of the antecedents are present, separated from the rest, and see what is the result of them; or to study other instances in which some only of the consequents present themselves, and find out which of the former antecedents existed and which were absent. In this way only is it possible to determine the *unconditional antecedent* or *cause* of a given consequent.

In order to "vary the circumstances" with this purpose in view, we must "interrogate Nature;" we may either wait until Nature in her ordinary course provides us with a suitable instance for observation, or we may contrive to produce the instance artificially—in other words, resort to *experiment*.

The pathologist who works with living human beings—be it in the hospital ward or in private practice—is dependent, as has been said, mainly upon his powers of observation. Some experiments he can perform, but these must be harmless and painless; and, as a rule, they have to be limited to procedures which will help to clear up the diagnosis and to measures which it is believed will be of therapeutic value.

The pathologist who works in the laboratory can supplement the results of observation by resorting to experimentation. His study of the human body is, it is true, confined to the examination of dead tissues or to the investigation of fluids or solids removed from the living; with animals, however, he is not so limited, but can study both the living and the dead, varying the circumstances at will.

It is of the utmost importance that the study of clinical pathology and that of laboratory pathology be intimately associated. Though through the division of labor it has become necessary that a man devote himself mainly to one or the other, still to be successful as a clinician much help is gained by prolonged experience in the methods of the laboratory, while to study pathology experimentally with hope of satisfactory results extensive preliminary clinical observations are highly desirable. If the two sides are divorced, there is an end of progress.

The clinician can only to a limited extent control his material; he has to observe the cases of diseases as Nature provides them to him; he cannot have a case presenting given phenomena at any moment he wants it, but, ever on the alert, must grasp as best he can the passing picture, preserving it as well as is possible in a clinical record. The experimental pathologist, when he has once established a definite relation of cause and effect with a given phenomenon, can reproduce that phenomenon at will and study it repeatedly by itself, or, by combining the causal antecedent with a variety of other antecedents, he can watch the modifications in consequents which result. He has, it is true, always to make his experiments from antecedent to consequent; he cannot directly experiment from consequent to antecedent. The starting-point of an experimental inquiry is nearly always an observation, but this need not always be so; on the contrary, experiments may be undertaken to test the validity of a theory or hypothesis.

How should one approach the study, then, of pathology? Observation should certainly precede experiment. It seems desirable, too, that there should be a certain sequence in the subjects of observation. Thus, in the wards the study of external pathology (clinical surgery) should precede the more difficult study of internal pathology (clinical medicine), and in the laboratory the pathology of the organs (gross pathology) should precede the pathology of the tissues and cells (pathologic histology). After a certain amount of empiric knowledge has been gained it is time to begin the interrogation of Nature—to trace the relations of antecedents and consequents, of cause and effect (pathogenesis and etiology). Here observation is still helpful, but experiment becomes infinitely more valuable. The complex phenomena of individual disease are gradually decomposed into

their simplest elements (special pathology), after which various diseases can be compared with one another, and, generalizing from multiple experiences, laws which hold for pathologic processes in general can be formulated, and the relation of them to the simplest laws of Nature can be established (general pathology).

While the above in general would seem to be the natural sequence of study and investigation, most find that they do well to make a circle of the sequence, traversing this circle at least several times. On each journey new view-points are attainable by virtue of previous experiences. Once well acquainted with the principal phenomena all around, residence for a prolonged period on some one part of the circle can more safely be indulged in.

The work which a pathologist accomplishes is dependent upon the quality of his mind and the opportunities available to him. All pathologists worthy of the name undertake original investigations. Only a few make great discoveries, but it is vouchsafed to many to make minor contributions to knowledge. The greatest minds devise new methods of work, new ways of approaching problems; lesser intelligences travel along the paths which genius has indicated, and make discoveries by applying the methods which genius has invented. Great minds provide the new ideas; lesser minds confirm them.

The beginner does well to associate himself with a master. A master will help him with rules for observing and with methods of interrogating Nature by observation and experiment. He will encourage him when in difficulty, and will hold him in check when he tends to a tangential course. Above all, by his example, he will afford him the greatest of all stimuli, that which lies in the demonstration that valuable results come only through patient, long-continued, rigorously controlled work.

GENERAL MORBID PROCESSES.

DISTURBANCES OF THE CIRCULATION.

Introduction.—The heart-muscle is an apparatus which transforms the chemical energy brought to it by the blood into the mechanic energy of muscular contractions and heat. The mechanic energy keeps the entire mass of blood in the body in constant motion throughout the blood-vessels, which form a system of closed elastic tubes. The blood forced into the arteries by the rhythmic contractions of the ventricles of the heart meets with a considerable degree of friction in the constantly narrowing arterial branches, and the resistance thus produced gives rise to the intravascular blood-pressure. This blood-pressure depends for its production and its degree upon the force of the heart's contractions and the amount of resistance in the arteries, the latter varying by virtue of the contractility of the arterial walls. Under normal conditions the force of the heart's contractions is so adjusted that, speaking in general terms, there ensues a gradual fall of hemodynamic pressure in the direction of the blood-current—namely, from the arterial to the venous orifices of the heart—and in this manner there is established a constant flow of blood throughout the arteries, capillaries, and veins.

The intravascular pressure varies from time to time within normal limits, depending upon the degree of arterial contraction. Under the regulation of the nervous system, the amount of blood sent to an organ is determined by the degree of local arterial tension, and is increased or diminished according as its cells are the seat of functional activity or of physiologic rest. And the blood by its own weight gives rise to a certain degree of purely hydrostatic pressure, which will vary according to the position of the body and the varying height of the column of blood supported by the vessels, especially the veins. But in health the nervous regulation of the tonic contraction of the vessels is so precise that the equilibrium of the circulation is not disturbed by changes in the hydrostatic pressure.

The circulation may be thrown into disorder in various ways. In the first place, there may arise general disturbances which affect all parts of the vascular system, and result in derangement of the onward movement and distribution of the general mass of blood and lymph. Then there are various local disturbances that only influence small vascular districts. Many local disorders react upon the circulation in general, but often in so slight degree as to escape observation.

GENERAL CIRCULATORY DISTURBANCES.

The general circulatory disturbances may arise (*a*) from conditions that interfere with the normal activity of the heart; (*b*) from diseases of the walls

of the blood-vessels; and (c) from changes in the amount and composition of the circulating fluids.

General Circulatory Disturbances due to Disorders of the Heart.—Normally the heart in a given time transmits the same amount of blood from each of its cavities. It is quite evident that if the left ventricle were to expel, for only a short time, one cubic centimeter less blood with each contraction than the other chambers, the blood would accumulate in the pulmonary circuit, and death would rapidly follow from the fall of pressure in the aorta. While momentary variations may occur, yet the amount of blood brought to the heart and the amount sent away must balance in the long run or life cannot be maintained.

Now, disturbances of the circulation due to diseases of the heart all depend upon derangement of the heart's function in the sense that less blood is transmitted than received. The diseases of the heart to be considered in this connection become dangerous to the degree that they diminish the product of the heart's labor—*i. e.*, the amount of blood sent out. Diseases of this kind may be situated in the valvular apparatus of the heart—the usual result of the various inflammatory processes in the valvular endocardium is to render the valvular orifice narrower than normal or the valves incompetent. Let us consider for a moment the effect of a permanent narrowing of the mitral orifice: the left auricle is unable to send through the narrowed orifice the usual amount of blood. The result is an accumulation of blood in the pulmonary circuit and a falling off in the amount that reaches the systemic circulation. A disturbance has been created in the onward movement of the blood, which, unless counteracted, is bound to become serious. If an aortic valve is incompetent, it allows some of the blood sent into the aorta during each diastole to regurgitate, the consequence being a diminution in the blood forwarded from the left ventricle. Indeed, so much blood may accumulate in the pulmonary circuit that the right heart is prevented from transmitting through the lungs the same amount that it receives, and there results a further massing up of the blood in the systemic veins. Similar effects would eventually follow stenosis or valvular inefficiency at any of the orifices of the heart. The general result of stenosis of an orifice or of incompetency of a valve will be, then, an accumulation of blood in the pulmonary or systemic veins—a general venous hyperemia—and a diminution of blood in the systemic arteries—an arterial anemia—due to the fact that less blood is sent away from the heart than is brought to it.

Diseases of the myocardium may have essentially the same effect. If for any reason, such as degenerative lesions in the heart's muscle, anemia, or other changes due to diseases of the coronary arteries, the contractions become irregular and enfeebled, so that the usual amount of blood is not sent into the arteries, it will follow that the pressure in the arteries sinks, while the blood accumulates on the venous side.

Diseases of the pericardium, accompanied by extensive adhesions between the two layers, or by the accumulation of fluid in the pericardial sac, cause serious disorder of the heart's action. In the case of adhesions these may be so strong as to prevent complete ventricular contraction, and in the case of fluid accumulations the pressure upon the heart may prevent full diastole. In either case the action of the heart becomes insufficient to keep up the equal distribution of the blood-mass, and venous hyperemia and arterial anemia result. Pressure upon the heart by undue elevation of the diaphragm, or

dislocation of the heart from this or other causes, may also result in cardiac insufficiency.

Continuation of circulation under these circumstances depends, first, upon the power of the circulatory system to adapt itself to variations in the amount of blood; and, second, upon the efforts of the heart to restore the circulatory equilibrium by undergoing a compensatory enlargement or hypertrophy. Thus, stenosis of the mitral orifice brings about, as stated, an accumulation of blood in the pulmonary circuit and a diminution of the amount sent into the aorta. By contraction of the arteries the arterial pressure remains practically unchanged, and in the meantime the wall of the left auricle grows thicker and stronger—undergoes hypertrophy—and perhaps becomes able to force as much blood through the narrowed orifice in its systole as enters the auricular cavity during the diastole. In a similar manner the heart, for a time, may compensate more or less fully for the insufficiency of its labor caused by disease at any of the valvular orifices. But an hypertrophied heart is always in danger of failure to meet the constantly increasing demands upon its toil, and sooner or later cardiac insufficiency develops in an aggravated form.

Chronic cardiac insufficiency results in congestion of the venous systems, because less blood is sent away from the heart than is brought to it; and yet at first the resulting arterial anemia is not so great but that by the narrowing of the arteries sufficient pressure is kept up to maintain the circulation. Usually an increased pressure develops in the dilated veins, which is followed by increased transudation from the capillaries and by edema. In consequence of the diminished amount of blood sent out from the left ventricle there is slowing of the circulation in the capillaries, increased accumulation of carbonic oxid in the blood, shown by a bluish discoloration of the skin—cyanosis—and also a fall in the temperature of the external surface. If the amount of blood sent into the aorta is very small, disturbances follow in the regulation of the arterial tonus, the arterial pressure sinks greatly, and the blood may accumulate in the veins and capillaries of the dependent parts of the body, giving rise to a bluish discoloration called hypostasis. Hypostasis indicates that the hemodynamic pressure has fallen so low that the blood in the dependent parts of the body obeys the law of gravitation only. These conditions signify that the cardiac insufficiency is extreme, and liable to be followed by a cessation of the action of the heart.

After death the tension of the vessels disappears; the arteries contract somewhat in consequence of their elasticity. Coagulation of the blood does not occur at once, and the fluid blood, following the law of gravitation, accumulates in the veins and capillaries of the dependent parts of the body. Some of the plasma is forced through the dead and consequently more permeable capillary walls, and the red corpuscles fall more closely together. The skin of such portions of the body becomes deep bluish-red and the tissues moist. The discoloration may be absent over portions of the dependent surface that are compressed over the bony prominences upon which the body rests. In the pulmonary circulation the hypostasis shows itself in the form of deep bluish-red, congested districts in the dependent parts of the lung, the tissue here being also infiltrated with serous fluid. Hypostasis likewise occurs in the veins and capillaries of the pia mater.

General Circulatory Disturbances due to Changes in the Blood-vessels.—The normal elasticity of the walls of the blood-vessels

is a most important factor in regulating the flow of blood. The arteries of the body support an uninterrupted, though periodically diminishing and increasing, tension; in many individuals the muscular coat is so perfect as to permit of a continuous tension during a long lifetime without becoming overstretched or dilated.

The most important disease of the vessels (angiosclerosis) with respect to the consecutive circulatory disorders is due primarily to diminution or loss of elasticity in the vascular wall. When the arteries lose their elasticity, dilatation of the lumen and growth of connective tissue in the intima follow (Thoma), so as again to reduce the size of the lumen to the normal. The wall is now thicker and stiffer than before, and the blood flows through a less yielding tube offering an increased resistance to the current. In order to overcome this increased resistance the heart, at first in the left and then also in the right ventricle, undergoes hypertrophy. If the extent of the arterial disease increases, so that the intima becomes rough and the wall irregularly dilated and thickened, the increased resistance to the current, aided by nutritive disorder of the heart-muscle, may lead to development of cardiac insufficiency and its consequences.

Under certain conditions the peripheral arteries may contract persistently and give rise to increased peripheral resistance. This occurs as a transitory manifestation in carbon-dioxid poisoning. In chronic inflammatory diseases of the kidneys permanent increase of pressure arises in the systemic circulation, due to arterial contraction from obscure and complex causes, and cardiac hypertrophy results.

Congenital narrowing of the aorta, large thrombi upon its walls, and compression by tumors may all give rise to hypertrophy of the heart.

A diminution in the total peripheral resistance to the current in the systemic circulation may be caused by a fall of the arterial tension, due to paralysis of the vasomotor centers. This occurs when the cervical part of the spinal cord is destroyed. The arteries dilate rapidly, the blood flows into the veins quickly, there is a decrease in the difference between the arterial and the venous pressures, the stream becomes slower and slower, and the heart is not able by its contractions to bring the blood-pressure up to normal. The blood-pressure may fall so low that the blood, following the law of gravitation, sinks to the dependent parts of the body and forms areas of hypostatic congestion. These phenomena can be studied upon animals after cutting either the cervical spinal cord or the vagus and sympathetic nerves, and then employing artificial respiration.

In the pulmonary circulation increased resistance to the current may be brought about by all those conditions that hinder respiration, such as pleuritic adhesions and curvature of the spinal column. Compression of the lungs by fluid accumulations in the pleural cavities, and diseases of the lungs accompanied by extensive destruction or removal of lung-substance and consequently of its capillary districts—emphysema, chronic interstitial and tuberculous processes—also cause obstruction to the circulation through the lungs. Such obstruction increases the pressure in the pulmonary artery and in the right heart, and gives rise to hypertrophy of the latter; if the hypertrophy cannot overcome the obstruction, passive congestion of the systemic venous circulation results.

General Circulatory Disturbances due to Changes in the Amount and Composition of the Circulating Fluids.—A gen-

eral acute anemia leads to a transitory fall in the aortic pressure, which rapidly rises again, if the loss is not too great, by the accommodation of the arterial tension to the reduced volume of blood (see Hemorrhage, page 50), and by a rapid restoration of the former volume of the blood-mass by an increased absorption of fluid from the tissue-spaces.

In chronic anemia (oligemia, oligocythemia) the arterial pressure is usually lessened and the blood-current is slowed. The absence of the normal amount of oxygen in the blood may lead to fatty and albuminous changes.

Hydremia, or hydremic plethora, an increase in the water of the blood, develops in chronic and acute diseases of the kidney, associated with a diminished excretion of water in the urine. It is usually associated with edema or dropsy, due to increased transudation through the changed walls of the capillaries and the accumulation of plasma in the tissue-spaces.

Anhydremia, or the diminution of water in the blood, occurs as a consequence of profuse watery evacuations in acute, severe intestinal catarrhal inflammations and in Asiatic cholera. It leads to the production of a small, slow pulse, due to the fall of arterial pressure, and also to diminution in the secretion of urine and saliva; the skin becomes dry and wrinkled, cold and cyanotic. These changes are in part attributable to the slowness of the circulation, in part to diminution in the total amount of circulating fluid.

PATHOLOGIC VARIATIONS IN THE LOCAL AMOUNT OF BLOOD.

The amount of blood required by an organ or tissue is subject to considerable variation within physiologic limits, according as the cells are functionally active or dormant. The regulation of the blood-supply under these circumstances is accomplished by changes in the caliber of the arteries, the smooth muscle-fibers of which contract or relax, as the case may require, under the influence of the vasomotor nerves, while the normal elasticity of the arterial wall maintains the necessary tone. An organ rich in blood is described as hyperemic, while one containing but little blood is spoken of as anemic.

When the amount of blood in an organ or limited vascular territory exceeds or falls below the physiologic limits, occurring independent of physiologic causes, or persists for an abnormal length of time, then the condition becomes one of pathologic hyperemia or anemia.

Pathologic hyperemia of an organ may result either from an excessive supply of arterial blood, in which case the state is known as arterial, active, or congestive hyperemia; or it may result from obstruction to the outflow of the venous blood, when the hyperemia is designated as passive, or venous.

Arterial, or Active, Hyperemia.—Active hyperemia is due to an increased supply of arterial blood. It may occur under a variety of circumstances, different causes producing dilatation of the arteries of a vascular territory either by paralyzing the vasoconstrictor nerves, by stimulating the vasodilator nerves, by directly weakening and paralyzing the muscular coat, or by removing or diminishing the extravascular pressure. The action of the following substances and conditions may lead to arterial hyperemia.

Chemicals.—When the frog's tongue or the mesentery of the rabbit is irrigated with a 1.5 per cent. salt solution, arterial dilatation and active hyperemia occur (Thoma¹). There are a number of medicinal substances,

¹ *Allg. path. Anat.*, p. 388.

such as alcohol, ether, ammonia, mustard, cantharides, etc., which when applied to the skin or mucous membranes cause local hyperemia. Some of these substances produce after more prolonged contact not merely simple hyperemia, but also hyperemia accompanied by exudative processes and the formation of vesicles.

Local Mechanic, Traumatic, and Thermic Influences.—It is within daily experience that scratching the skin produces red areas. In certain diseases of the nervous system, such as *tabes dorsalis*, meningitis, etc., also in exophthalmic goiter, very light strokes often suffice to produce red stripes and spots (dermographia in exophthalmic goiter; *tâches cérébrales* in meningitis). In these experiments the irritation of the skin produces circumscribed arterial hyperemia by modifying the vasomotor innervation. The exact mechanism by means of which the hyperemia is produced is not clearly understood, but the fact that in diseases of the central nervous system hyperemic areas so easily appear would seem to indicate that the local irritation of the skin acts in a reflex manner.

More severe trauma also produces local arterial hyperemia, usually accompanied by further changes, that are considered elsewhere. Moderate heat when applied to the skin leads to vascular dilatation and hyperemia, even when the nerves connecting the arteries with the cerebrospinal vasomotor centers have been completely severed.

Local anemia, when not altogether too evanescent, is usually succeeded by arterial hyperemia. Local anemia produced by the application of cold is regularly followed by a brief hyperemia when the normal temperature of the part is again restored. The removal of long-continued pressure upon blood-vessels is also succeeded by arterial dilatation and hyperemia, which may give rise to a secondary, or collateral, anemia elsewhere in the body; the collateral cerebral anemia occasionally produced may give rise to fainting. This is sometimes the result of the great hyperemia of the blood-vessels of the abdomen that develops when large fluid accumulations are suddenly removed by tapping, unless the pressure previously exerted by the fluid is in a measure replaced by means of a tight abdominal bandage. The production of arterial anemia in practical surgery by the application to an extremity of an Esmarch bandage is succeeded by arterial dilatation after the removal of the constrictor.

The closure or narrowing of an artery leads to a collateral hyperemia of neighboring areas (page 44).

Paralysis of the vasoconstrictor nerves produces a pure arterial hyperemia. Cutting the sympathetic nerve in the neck of animals is followed by arterial dilatation and redness in the corresponding half of the head and neck: wounds and pressure by tumors, glands, etc., have the same effect in man. Reflex vasomotor influences of various kinds also lead to hyperemia, as, for instance, in blushing.

In consequence of the dilatation of the arteries in active hyperemia, the blood-current meets with less resistance than normally, and a greater amount of blood flows through the hyperemic area. The pressure in the corresponding capillary district rises as the blood remains under a greater hemodynamic pressure, on account of the diminished peripheral arterial resistance. In this way may be explained capillary and venous pulsation, which is sometimes observed in actively hyperemic parts. The rise of pressure in the capillaries leads to dilatation of the latter, and a diffuse redness develops.

The exact influence of hyperemia upon the process of transudation has not yet been determined. Emminghaus states that in occasional instances there was an increased production of lymph in the dog's leg, made hyperemic by cutting the sciatic nerve.

During life the hyperemic area is of a more or less deep-red color, and, if located upon the surface of the body, is warmer than its surroundings; but arterial hyperemia is not demonstrable after death.

Local Venous Hyperemia.—Local venous hyperemia, or passive congestion, arises from obstruction to the outflow of the blood from the veins of an organ or vascular territory. It may be part of a general venous congestion due to central causes, located in the heart, mediastinum, or lungs; or it may depend upon purely local circumscribed conditions.

Among the various causes of strictly local passive hyperemia may be mentioned external compression of the veins by tumors, aneurysms, contracting cicatricial tissue, inflammatory swellings, and ligatures; occlusion of the lumen of the veins by ingrowing tumors, by thrombosis, and, in rare instances, by embolism; increased pressure in the abdominal cavity by large tumors, excessive ascites, and by the pregnant uterus.

In all these instances the general effect of the obstruction will naturally vary, depending upon the degree and the anatomic seat of the hindrance, and upon the absence or presence of collateral routes along which the returning venous blood, circumventing the obstruction, may reach the heart. If the occluded vein communicates quite freely with other veins, then the obstruction will cause at most only a temporary overfilling of the veins drained by the blocked vessel, the blood soon finding exit by way of the communicating branches. But if the obstructed vessel possesses insufficient or perhaps no communications with other veins, then the phenomena of passive congestion will develop to the fullest degree. Among veins and venous channels belonging to the latter group may be mentioned the splenic, the renal, the femoral, and the portal vein, and the sinuses of the dura mater.

The phenomena of passive congestion can be observed by making the following experiment (Cohnheim¹): A frog is curarized and the two lateral veins of the tongue ligated near the root of the latter; in this way all the collateral branches are shut off. The appearances can now be studied from time to time by spreading the tongue out, and fastening it by means of pins to strips of cork glued to a glass slide. At intervals the tongue should be returned to the mouth, lest excessive vascular changes occur. Marked congestion rapidly develops; the veins and capillaries dilate; the tongue becomes dark red; the distinction between the axial and the peripheral currents in the veins is lost. These and the capillaries become crowded with closely packed red blood-corpuscles, whereas the blood-plasma seems to disappear, while the tongue becomes slightly swollen. In the course of a few hours the blood has stopped in the veins and capillaries—*stasis*—and a few red corpuscles have found their way out of the vessels into the surrounding tissue-spaces—*diapedesis*; while in the arteries the blood-mass presents oscillatory movements synchronous with the pulse. Here and there near the root of the tongue are seen greatly dilated capillaries, hitherto invisible, through which the blood very slowly finds its way into the unobstructed veins, thus relieving in a small degree the congestion. According to Thoma

¹ Virchow's Archiv, xli., 1867.

and Zielenko, the arteries are not dilated, but contracted, in this and similar experiments.

From experiments and clinical observations it has been learned that obstruction to the venous outflow causes first a slowing of the current in the veins and the capillaries on the distal side of the hindrance. The slowing of the current lessens the resistance due to friction; hence, less hemodynamic pressure is consumed, and a rise of pressure ensues in the veins and capillaries of the congested area, causing them to dilate. The increased pressure favors transudation of serum, and this may occur to such an extent that the lymph-vessels are not able to carry away the transudate accumulating in the tissue-spaces, and a condition of edema, or dropsy, develops. The contraction of the arteries in the congested area is secondary to the diminished amount of blood that flows through this area in a given time; it tends to prevent an excessive rise of pressure in the veins and capillaries, and to limit the amount of transudation, while the collateral veins are given time to dilate, and thus to relieve the congestion.

In passive hyperemia of an extremity the tissues become swollen on account of the dilatation of the capillaries and veins and the increased transudation; the cutaneous surface is cool, because less blood passes through the congested part and less heat is brought to it; a bluish discoloration of the skin, so-called cyanosis, develops, because the blood in the capillaries is rich in carbonic oxid by reason of the sluggish circulation. These conditions may persist for a long time, especially when the hyperemia is of central origin, and may result in thickening and increase of the subcutaneous, intermuscular, and even periosteal connective tissue.¹

In the internal organs moderate degrees of passive congestion of short duration do not, as a rule, produce permanent changes. When of long duration the pressure of dilated capillaries upon adjacent cells may cause a degenerative atrophy. Diapedesis of red blood-corpuscles may also take place, followed by disintegration and the setting free of pigment-granules. Under these circumstances some increase of the connective tissue generally results.

The severest form of passive congestion develops from occlusion of all the efferent vessels of an organ or an extremity. Here the rise of pressure in the veins and capillaries may equal the pressure in the arteries. All the plasma of the blood may pass out into the tissues, and complete stasis or stoppage of the blood-flow may result. The changed capillary walls favor diapedesis, and the tissues become the seat of a bloody infiltration, or hemorrhagic infarction, followed by death of the hemorrhagic area. Decomposition, or moist gangrene, may develop in the dead tissues.

Complete closure of all the veins of an organ may occur in the case of the spleen, liver, or kidney, in consequence of thrombosis or retrograde embolism. In a case of complete thrombosis of all the veins of the spleen observed by the writer, hemorrhagic infiltration and necrosis of the entire organ ensued. When branches of the splenic (Sokoloff) or renal (Litten) vein are ligated, circumscribed necrotic areas are formed that become infiltrated with blood, just as in the case of hemorrhagic infarcts due to arterial occlusion. Arnold demonstrated that retrograde embolism of the hepatic vein gives rise to hemorrhagic infarction in the liver.

¹ The student can readily observe the ordinary initial phenomena of passive congestion in an extremity by encircling a finger with a tight rubber band: the coolness, the swelling, and the discoloration all occur.

In strangulated hernia the imprisoned loops of intestine become the seat of a marked passive congestion which may be succeeded by stasis, hemorrhagic infiltration, and necrosis.

In the case of the portal vein certain anomalous conditions are presented, because of its breaking up into capillaries within the liver before emptying, by way of the hepatic veins, into the vena cava. Obstruction to the blood-flow in the portal vein may occur not only in the course of the vein proper, but also in the substance of the liver. While sudden occlusion of the portal vein in animals is almost immediately fatal, in man sudden closure from thrombosis is not followed by rapid death. The pressure in the vein rises rapidly, the branches and radicles dilate excessively, large quantities of serum transude into the abdominal cavity, the spleen increases to three or four times its normal size, watery discharges take place from the bowels, and death finally occurs from exhaustion. In some of the forms of cirrhosis of the liver the contracting fibrous tissue compresses and destroys the portal branches and capillaries, so as to cause obstruction and passive congestion of the portal vein and its radicles. Usually this occurs so slowly and gradually that in many cases a collateral circulation has time to develop by means of the rather inconstant anastomosis between radicles of the portal vein and the esophageal, hypogastric, and other veins; in the majority of instances, however, the pressure remains high enough to result in ascites and in marked congestion of the spleen and the gastro-intestinal tract.

In the lungs chronic passive congestion, with induration and pigmentation, may follow disease in the mitral valve or insufficiency of the muscle of the left ventricle.

Local Anemia (Ischemia); Collateral Anemia; Infarction.—

Local anemia is due to a diminished amount of blood in a vascular territory. It may be part of a general lack of blood in the body, or it may depend entirely upon local causes, such as external compression of the arteries and capillaries, narrowing or closure of their lumen from changes in their interior, or increase of the normal peripheral resistance to the current by contraction of the circular muscular coat. Thus, local anemia is produced by compressing the vessels of an extremity with an Esmarch bandage, by the pressure of a tumor, of an extensive inflammatory exudate, or of contracting cicatricial tissue on the arteries. Or it may follow the narrowing or occlusion of the lumen of an artery by inflammatory thickening of its walls (endarteritis), by the formation of thrombi, or of the lodgement of emboli in its interior.

Disturbances of the vasomotor innervation often produce local anemia, as shown, for instance, by the bloodless condition of the body surface when exposed to cold. Brown-Séquard showed that stimulation of the cervical sympathetic is followed by contraction of the arteries of the same side of the head. A so-called collateral anemia, due to arterial contraction, usually develops in the vicinity of areas in which arterial dilatation and hyperemia prevail, and in the case of excessive active hyperemia of an organ or part distant parts may become anemic. Under such circumstances the total quantity of blood is not sufficient to fill all the vessels to the usual extent.

Local anemia produces paleness of the affected tissues. The narrowing of the arteries increases the resistance to the current, and in order to overcome the resistance more hemodynamic pressure is used, and the blood reaches the capillaries under lower pressure; the capillaries contract in consequence of their elasticity and the fall in pressure, and the total quantity of blood in the

area diminishes. In the skin the anemic part is of a lower temperature than the surrounding integument, because with the lessened amount of blood less heat is brought to the surface.

Anemic conditions produced by tonic contraction of the arteries are usually temporary in duration; but the occlusion due to ligatures, thrombosis, or embolism, being often permanent, results in nutritive disturbances or the formation of new routes for the circulation.

According to Thoma and Nothnagel, occlusion of an artery leads to arrest of the circulation in the area after the vessel has emptied itself; the pressure rises a little from the point of the obstruction back to the nearest arterial branch. If the branches distal to the obstruction possess free communication with an unobstructed artery, the latter becomes somewhat dilated, and the circulation is soon restored through the area nourished by the occluded vessel. The rapidity and the completeness with which the collateral circulation develops depend upon the size and capacity for dilatation of the branches that are in communication with the vessels of the anemic area. If numerous and large, the circulatory disorder is soon obviated. If this be not the case, then more complex, but exceedingly interesting, changes of adaptation develop. A contraction of the occluded artery occurs proximal to the point of obstruction; in the collateral arteries increased rapidity of the current and dilatation of the lumen take place, giving rise to a vicarious hyperemia. The vessels through which the collateral circulation is being established soon show actual increase not only in the thickness of their walls, but also in length, becoming somewhat convoluted; while the central, patent part of the occluded artery becomes the seat of a concentric atrophy, with narrowing of the lumen. In other words, the intravascular pressure is readjusted so as to favor the development of collateral circulation; while in the arteries such structural changes take place as render them best adapted to meet the new requirements.

The mechanism of these changes is in part as follows: When a main artery is ligated the blood flows with little resistance from the capillaries of the anastomosing branches into those of the ligated artery, the result being an increased rapidity of flow in the anastomosing vessels (von Recklinghausen). The resulting changes in the walls of the arteries are best interpreted as referable to a genuine work-hypertrophy (Welch).

It has also been shown that new anastomoses may be formed by the capillaries, which dilate and gradually acquire the structure of arteries. Even veins may be forced into service: the blood above a ligature flows into a capillary district, and thence into a vein, which again allows the blood to pass into the capillaries of arterial branches below the ligature.

Under certain special local conditions the closure of an artery fails to be followed by an efficient collateral circulation, and the consequence is that the part formerly nourished by the occluded vessel undergoes necrosis due to ischemia. It is in the organs supplied with so-called *terminal arteries* (Cohnheim¹) that anemia has this result (see page 72, concerning embolism in this connection). An end-artery, or terminal artery, is an arterial branch which supplies a definite portion of an organ, and has no anastomosis with neighboring branches. Such arteries are found in the spleen, the myocardium, the kidney, the brain, certain parts of long bones, and the retina. The superior mesenteric artery and pulmonary arteries also possess imperfect

¹ *Virchow's Archiv*, lxx., 1875.

collateral communications, and act, particularly under special conditions, as virtual terminal arteries.

The anemia resulting from occlusion of a terminal artery leads to death of tissue, in some organs earlier, in others later: ganglion-cells, renal and intestinal epithelial cells perish if the circulation is interrupted for two hours; while skin, bone, and connective tissue may live without blood-supply for twelve hours or longer. The areas of anemic necrosis following the occlusion of terminal arteries are called *infarcts*. They are most typical in the spleen and in the kidney; here they present a pyramidal or wedge-shaped outline, the base corresponding to the surface of the organ, the apex pointing inward. At the point is usually found the plugged artery (Figs. 1, 2).



FIG. 1.—Anemic embolic infarct in the cortex of the kidney. The embolus was a small thrombic mass detached from a heart-valve the seat of inflammation.



FIG. 2.—Irregularly pyramidal-shaped anemic infarct in the spleen, with softening about the apex, due to embolism of the splenic artery.

On the cut surface the infarct presents an opaque, yellowish-white appearance; microscopically, in stained sections, the nuclei of the cells are found wholly or partially unstained—necrosis, or death, has occurred.

As long as the infarct remains bloodless it is designated an anemic, or white, infarct, in contradistinction to the red, or hemorrhagic, infarct which is produced when blood reenters the previously bloodless area. This blood does not come, as a rule, from arterial anastomosis, but from neighboring capillaries; regurgitation from the veins probably does not occur. The fact that this blood appears in the area of anemic necrosis may be regarded as of the nature of an effort to establish a collateral circulation, but the obstacles are so great that in the meantime the tissues die; furthermore, the interruption of the circulation results in such alterations of the capillary walls that all parts of the blood, solid as well as fluid, pass out and infiltrate the surrounding dead tissue. In this way the hemorrhagic infarct is produced. Even should the blood enter the capillaries of the anemic area early, the low pressure under which it is insufficient to reestablish the circulation. According to Thoma, the blood is prevented from entering the vessels of anemic areas in the spleen by the temporary tonic contraction of the smooth muscular fibers in the trabeculae of the organ.

Some infarcts are only partly hemorrhagic, for the dead tissue may offer so much resistance to the flow in the capillaries that it is arrested; this is frequently observed in the kidney. According to Litten, hemorrhagic infarcts may develop in the kidney after ligation of the corresponding vein, showing that the blood in question must come from the surrounding capillaries.

In the brain, occlusion of the smaller vessels beyond the circle of Willis is followed by necrosis, with liquefaction or softening of the brain-tissue. These areas of softening may present variations in color, depending upon small hemorrhages into the necrotic tissue from the surrounding capillaries.

The superior mesenteric artery anastomoses to a certain extent with the inferior mesenteric and with the gastroduodenal arteries; but these anastomoses are not sufficient to reestablish after occlusion the circulation with sufficient rapidity to maintain the integrity of the capillary walls (Litten).¹ The anemia, aided by the action of the intestinal bacteria and their toxic products, results in extensive necrosis; and when blood enters by way of the collateral channels mentioned hemorrhagic infiltration of a large part of the intestine develops. Peritonitis, septic intoxication, and death may follow. The slower occlusion of the artery by thrombosis may give the collateral circulation greater time to develop, and such extensive necrosis may be in part, or even wholly, prevented. Hemorrhagic infarction and necrosis of the small intestine are also observed in connection with thrombosis of the portal or the mesenteric vein (Riesman).²

The coronary arteries of the heart also possess collateral branches that are insufficient to prevent anemic necrosis of the heart-muscle following occlusion due to embolism, thrombosis, or other causes. Some hemorrhage usually occurs into the necrotic and softened tissue.³

In the lungs hemorrhagic infarcts (Fig. 3) occur most readily under special local conditions, namely, when the lung is the seat of passive

congestion, which is most frequently due to disease of the mitral valve. In that case embolism or thrombosis of the pulmonary arteries gives rise to infarction. The pressure of the blood in the adjacent capillaries, which under ordinary conditions may be sufficient to restore the circulation through the obstructed area, is unable to overcome the greatly increased venous pressure due to the valvular disorder, and stasis, transudation, diapedesis,

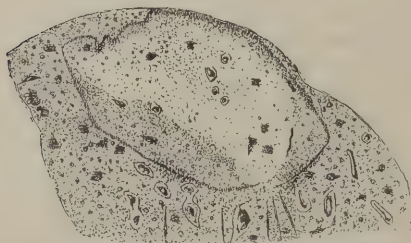


FIG. 3.—Irregularly wedge-shaped embolic hemorrhagic infarct in the lung, following thrombosis in the right auricle, in a woman with mitral stenosis. The border is sharp; the area quite homogeneous and red.

and hemorrhage occur. In very rare instances pulmonary infarcts are anemic in consequence of extreme weakness of the circulation (Welch).

Hemorrhagic infarction and necrosis of the uterus may follow bilateral embolism of the hypogastric arteries or bilateral thrombosis of the uterine veins (Chiari).⁴

Anemic and hemorrhagic infarcts are most frequently produced by embolism. In case the embolus is infected suppuration usually occurs. The consequences of infarction due to aseptic emboli depend upon the part affected: if in the brain, the retina, the heart, etc., serious functional disturbances may follow. The further changes are those of absorption and replacement with connective tissue (Fig. 4) or, in the case of the brain,

¹ *Virchow's Archiv*, lxx., 1875.

³ *Prag. med. Woch.*, 1896.

² *Proc. Path. Soc. Phila.*, vol. ii., N. S.

⁴ Baumgarten, *Am. Jour. Phys.*, 1899.

cyst-formation. Extensive infarcts too large to be absorbed may become calcified and enclosed in cicatricial tissue.

STASIS.

Stasis develops when the blood in the capillaries loses all its plasma. The capillary lumen becomes distended with a homogeneous, dark-red column or mass of red blood-corpuscles, which are so closely crowded together that the contour of the individual corpuscles is no longer distinguishable. Thrombosis as a rule does not occur, and the red corpuscles do not coalesce into one mass; and when the conditions that resulted in stasis are removed and plasma again enters the capillaries the corpuscles gradually separate from one another, so that the normal blood-current is soon restored.

Stasis arises under a number of different conditions that are usually connected with the various forms of local circulatory disturbances. Thus, excessive passive hyperemia due to complete obstruction to the venous current

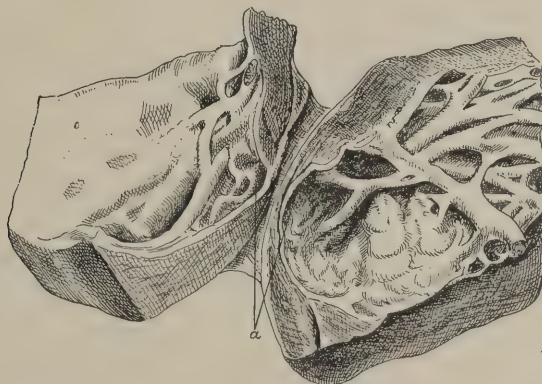


FIG. 4.—Absorption of necrotic tissue, due to arterial occlusion in the wall of the left ventricle, the formation of connective tissue, and beginning bulging of the wall at the weak place (a).

will result in such dilatation and rise in pressure in the capillaries, veins, and arterioles of the congested area that the blood-plasma is pressed out through the capillary walls into the meshes of the tissue (edema), while the red corpuscles come into closer and closer apposition.

In inflammation and in local anemia following embolic and other forms of arterial occlusion, stasis also develops as a result of nutritive changes in the capillary walls, which present such increased permeability that the plasma pours out from the vessels.

Stasis may be produced by the action of chemical and other influences upon the tissues. Thus stasis may result from evaporation and drying of tissues that are brought out from the interior of the body and exposed to dry air. Cold and heat may cause stasis; so also the action of acids and alkalis, of chloroform and alcohol, of croton oil, etc. These substances may act in different ways: by abstracting water, by changing the capillary walls so as to increase their permeability, or by making the red blood-corpuscles viscid. Concentrated solutions of sugar and of salt (5 per

cent.), when applied to the tongue or mesentery of frogs, produce stasis by removing the water from the circulating blood (Wharton Jones,¹ von Recklinghausen).

HEMORRHAGE.

Hemorrhage is the exit of the blood from the circulatory channels. It may occur from the capillaries, veins, arteries, or the cavities of the heart; and the blood may escape externally upon the skin, into mucous or serous cavities, or into the interstices of the tissues.

The blood may pass out from the vessels in two ways, either by diapedesis or by rhexis (diabrosis). *Diapedesis* is the passage of the red blood-corpuscles and of the plasma through the unruptured walls of capillaries and minute veins. Hemorrhage by *rhexis* is hemorrhage in consequence of mechanic solution of continuity of the vessel-wall; it is the only way in which hemorrhage can take place from the heart, the arteries, and the larger veins. From the minute veins and the capillaries bleeding may occur in either way.

In order to study the process of diapedesis, a vein in the mesentery or tongue of a curarized frog may be ligated, so as to produce passive congestion and stasis (Cohnheim). After a certain time the red blood-corpuscles begin to pass out from the capillaries and venules into the surrounding tissues. The microscopic appearances of the capillary walls in the living animal do not present any deviations from the normal under these circumstances. If the ligature, the cause of the stasis, be removed and the circulation allowed to become natural again, the details of the process can be studied even better than before. The red cells are noticed not only in the tissues, but also in the capillary walls, where they are seen, either singly or in groups, lying compressed in small openings. From time to time a corpuscle will be seen to attach itself to the inner surface of a capillary, a fine process passing outward through the wall. As the extravascular process becomes larger the intravascular part becomes smaller and smaller, until finally the whole corpuscle has passed through into the tissues, where it soon resumes its normal form. Only a few corpuscles become broken into fragments, the majority pass through uninjured. A few white cells and some blood-plasma also pass out.

Thoma has observed that in warm-blooded animals even a thicker blood-stream may pour out through an opening in the capillary wall, which immediately closes itself again. In consequence of such streaming out by diapedesis quite extensive areas of hemorrhage (ecchymoses) may form in the mesentery.

Diapedesis was first observed by Stricker and by Cohnheim; subsequently it was studied by Arnold,² whose investigations disclosed the finer details of the process. Arnold injected silver-nitrate solutions into capillaries the seat of diapedesis, and found that at points the silvered borders of the endothelial cells presented changes which he regarded as minute openings, called stigmas, or stomas. Subsequently he regarded these points as due to a greater accumulation of cement-substance between the endothelial cells, and concluded that diapedesis occurs as a consequence of an increased permeability of the capillary wall, best explained as due to a loosening of the intercellular cement-substance. Inasmuch as the red blood-corpuscles are

¹ *Guy's Hosp. Reports*, 2d series, vii.

² *Virchow's Archiv*, lvi., 1875.

immobile, it would seem that they are pressed through the capillary wall by the intracapillary blood-pressure.

Hemorrhage by diapedesis may reach a considerable extent, especially when it takes place in a large area and continues for a long time.

Diapedesis occurs frequently in consequence of local circulatory disturbances which produce changes in the vascular walls, namely, in local anemia with subsequent formation of hemorrhagic infarction (page 45), in passive congestion and stasis, and also in inflammation. Diapedesis, furthermore, accompanies a number of general infections, intoxications, and nutritive disturbances, in which frequent spontaneous hemorrhagic extravasations indicate a widespread abnormal permeability of the capillary walls.

Hemorrhage by rhexis, or tearing of the vascular wall, may take place either spontaneously or in consequence of traumatism. Injuries of various kinds may give rise to hemorrhage by immediate severing of the walls of the vessels, as well as of the heart. Extensive and complex traumatisms, accompanied by twisting and distortions of the body, are often the cause of hemorrhage far removed from the location of the direct injury. Such hemorrhages may be either capillary, venous, or arterial, according to the kind of vessel affected; in a large number of conditions the blood comes from all three divisions at the same time. The so-called parenchymatous oozing which occurs from the surface of an operative wound after the larger vessels have been ligated is a good example of traumatic capillary hemorrhage. When blood escapes externally from an artery it spurts forth intermittently, whereas from a vein the flow is more continuous. The extent of an unimpeded traumatic hemorrhage will depend upon the size of the severed vessels as well as upon the extravascular conditions. Thus a small vessel upon the surface of a large cavity will give rise to more bleeding than a similar vessel in the interior of a solid organ, where the pressure after a time may be sufficient to arrest further flow.

In persons suffering from hemophilia (see below) insignificant wounds may be followed by persistent, sometimes uncontrollable, hemorrhage.

Spontaneous hemorrhage occurs in consequence of excessive rise in the blood-pressure, and as the result of diseases of the vascular walls. While increase in the intravascular pressure may cause rupture of a healthy capillary wall with capillary hemorrhage, it is the general opinion that increased intravascular pressure alone is not sufficient to rupture healthy, fully developed arteries and veins. Diseased blood-vessels may, of course, rupture under the normal vascular pressure; but a sudden increase of the pressure is the common exciting moment in the bursting of a pathologic vessel. Newly formed vessels, as in granulation-tissue and in sarcoma, break very easily.

The morbid changes which diminish the strength of vessels may develop primarily in the walls of the vessels, as inflammation, sclerosis, aneurysm, and fatty degeneration; or they may invade the wall from without, as is seen in various inflammatory and destructive processes. Hemorrhage produced in the latter instance is sometimes referred to as hemorrhage by diabrosis; a



FIG. 5.—Silvered capillary of a frog after diapedesis (Arnold).

good example is the hemorrhage of pulmonary tuberculosis, which is often caused by the rupture of a vessel the wall of which has been weakened by tuberculous invasion. Cerebral apoplexy, or hemorrhage into the brain, is a frequent and very important example of bleeding due to the rupture of arteries the walls of which have become weakened by primary disease.

Any sudden rise of intravascular pressure, such as may be caused by a comparatively unimportant trauma, straining at stool, sudden physical exertion, or fright, may precipitate the rupture of such weakened structures; and when a constant increased arterial pressure exists, as in chronic nephritis and hypertrophy of the heart, the danger of rupture of a diseased blood-vessel is always imminent.

Fatal hemorrhage may be caused by rupture of the heart, following softening or fatty degeneration of its muscle.

Certain individuals present a remarkable inherited or acquired tendency to hemorrhages, which is known as the hemorrhagic diathesis. In the hereditary form, termed *hemophilia*, or bleeders' disease, extensive, persistent, and sometimes uncontrollable hemorrhages follow traumatic lesions that in healthy persons give rise to but a transient and insignificant loss of blood. Protracted spontaneous hemorrhages also occur. The characteristic feature of hemophilia is not only the great tendency to bleeding, but also the absence or failure of arrest of hemorrhage by vascular contraction and thrombosis, which occurs in all smaller hemorrhages in the healthy. While the causes of hemophilia are unknown, theoretically the existence of abnormally constructed blood-vessels, as well as of a changed composition of the blood, causing a diminution in its coagulability, would explain the increased tendency to and the persistence of the bleeding.

Acquired hemorrhagic diathesis presents itself first as one of the essential manifestations of apparently primary diseases (scurvy, morbus maculosus Werlhofii, purpura hemorrhagica), characterized by hemorrhages into the skin, the serous and mucous membranes, and the parenchymatous organs. The etiology of these diseases is not yet definitely established, and for the present the tendency to hemorrhage must be assumed to be due to changes in the blood-vessels, produced by toxic substances of unknown, possibly bacterial, origin, and perhaps associated with diminution in the coagulability of the blood.

Acquired hemorrhagic diathesis also appears in a more or less pronounced form as a secondary manifestation in a number of infections (septicæmia, cholera, small-pox, endocarditis, anthrax, typhus fever), intoxications (snake-bite, phosphorus poisoning), and chronic diseases accompanied by grave disorders of nutrition (carcinoma, chronic nephritis, leukemia and other blood diseases). In these diseases spontaneous ecchymoses and larger extravasations appear in various parts of the body. They must be attributed to nutritive disturbances and changes in the vascular walls, especially of the capillaries, due in some instances to a direct microbial implantation; in others to an impaired composition of the blood.

There are some hemorrhages that are ascribed to changes in the vasomotor innervation of the vessels, and are consequently designated *neuropathic*. This applies to the hemorrhages of vicarious menstruation (nose, digestive tract, skin, mammary glands), as well as to hemorrhages into the skin, conjunctiva, and other mucous membranes in hysterical persons (hysterical stigmas). Furthermore, many severe cerebral lesions are accompanied by

gastric, intestinal, adrenal, or pulmonary hemorrhages, which seem to stand in some direct relation to the nerve-changes. Brown-Séquard, Vulpian, and others observed such hemorrhages after operations upon the brain and spinal cord; but the exact mechanism by means of which these hemorrhages are produced has not been demonstrated.

The spontaneous hemorrhages of the hemorrhagic diatheses and the hemorrhages of neuropathic origin are undoubtedly largely of a capillary nature; but whether produced by rhexis or by diapedesis cannot be definitely stated, although it is probable that diapedesis is to a large extent responsible.

It is customary to distinguish by special names the hemorrhages that occur from free surfaces, into serous or other cavities, and into the substance of organs. Hemorrhage from the nose is known as epistaxis, from the respiratory tract as hemoptysis, from the stomach as hematemesiis, from the intestines as melena, from the uterus as metrorrhagia (profuse hemorrhage during menstruation as menorrhagia), and from the urinary organs as hematuria. Effusion of blood into the pericardium is designated as hemopericardium, into the pleural cavity as hemothorax, into the tunica vaginalis testis as hematocele, into the uterus as hematometra, into the Fallopian tubes as hematosalpinx. Hemorrhage into the spinal cord is termed hematomyelia. When hemorrhage occurs into the interstices of tissue in the form of small punctiform foci, it is known as ecchymosis, or petechia. When the extravasation is more extensive, not sharply circumscribed, and rather flat, it is spoken of as suggillation, or hemorrhagic suffusion. When the blood firmly infiltrates the tissue the condition is one of hemorrhagic infarction (see page 45); and when a roundish, tumor-like mass of blood accumulates in the subserous or subcutaneous connective tissue, it is sometimes called a hematoma.

The consequences of hemorrhage depend upon the quantity of blood lost, upon the place where the hemorrhage occurs, and upon the further changes that take place in the extravasation.

In the first place, hemorrhage, either external or into the larger body-cavities, may be accompanied by the loss of so much blood that death ensues from the great fall of pressure in the arteries or from cerebral anemia. The circulatory system is, however, able to provide, within certain limits, against the immediate dangers of hemorrhage. It has been shown that in the dog the pressure in the aorta remains unchanged so long as no more than from 2 to 4 per cent. of the body-weight of blood is removed—2 per cent. in the case of sudden, 4 per cent. in the case of more gradual, loss. Thoma¹ calculates that in man almost one-half of the normal quantity of blood may be lost from hemorrhage without either marked or permanent fall in the aortic pressure. It is estimated that the loss of blood to the extent of more than 3 per cent. of the body-weight is dangerous, and rapid losses from large arteries may cause death even before this limit has been reached. Great variations are presented in the different ages and sexes and by different individuals.

The dangers from the loss of blood are met in part by the readjustment of the vascular tonus—as the blood is removed the arteries contract, so that the pressure in them remains unchanged—and also by the increased absorption into the blood-vessels of fluid from the tissues and lymphatic channels, so that during hemorrhage the relative quantity of water in the blood—*i. e.*, its volume—increases. In this way the dangers from rapid fall of pressure

¹ *Untersuch. über die Histogenese und Histomechanik des Gefässsystems*, 1893.

are obviated to a certain degree. Furthermore, Alexander Schmidt has shown that during hemorrhage the coagulability of the blood increases; this favors thrombosis and arrest of the hemorrhage. The development of thrombosis is also aided by falling of the blood-pressure.

Further changes that have for their purpose the regeneration of the blood are considered elsewhere.

Serious consequences may also follow hemorrhage on account of the place where it occurs. Thus, a sudden hemorrhage into the pericardial cavity, though not at all dangerous on account of the quantity of blood lost, may produce death by direct pressure of the blood-mass upon the heart; and hemorrhages into the brain, which are always accompanied by more or less tearing and destruction of tissue, are dangerous to life not only on account of the possibility of demolishing certain vital nervous centers, but also on account of the great increase in the intracranial pressure to which the extravasated blood gives rise; hemorrhagic extravasations into or behind the pancreas may cause sudden death from pressure upon the solar plexus. In persons who have been subject to long-continued small losses of blood, as from tumors of the bladder, a sudden larger hemorrhage may prove fatal.

The subsequent changes in the extravasated blood are essentially those of removal and absorption. After hemorrhage into the serous cavities the blood may remain fluid for some time, especially in the pleural and the peritoneal cavities, and considerable absorption of the fluid blood may occur. After a time, however, coagulation usually takes place. Considerable diffusion of hemoglobin now occurs, and the surrounding tissues become temporarily bluish-green. Broken-down as well as entire red corpuscles are taken up by leukocytes and carried away. Part of the hemoglobin is transformed into various kinds of crystalline and amorphous pigments (see Pigmentation), which are carried away by leukocytes or remain where formed, the bluish-green color gradually changing to yellow and finally disappearing. The dead white cells and the fibrin undergo fatty and other obscure chemical changes that are accompanied by varying degrees of softening. In the meantime the surrounding connective tissue proliferates, numerous leukocytes are attracted to the clot, and it finally becomes more or less completely absorbed and replaced by newly formed connective tissue which subsequently changes into a pigmented cicatrix. The regional lymph-glands are usually swollen and filled with leukocytes containing detritus removed during the absorption of the clotted blood. In some localities, especially in the brain, the softening of the coagulated blood and tissue-detritus is followed by the removal of the solid particles, while the fluid becomes enclosed in a sac of connective tissue, constituting a so-called apoplectic cyst. In some cases partially absorbed clots in the interior of tissues become calcified; or a microbial infection may occur, and the softened and changed extravasation becomes mixed with pus.

LYMPHORRHAGE.

Lymphorrhage, or extravasation of lymph, does not occur so frequently and is not so important a process as hemorrhage. It arises as the result of solution of continuity in the course of lymph-vessels. Inasmuch as the pressure in the lymph-vessels is not much greater than that of the surrounding tissues, it follows that extensive extravasations of lymph can take place only externally or into the larger cavities. In large wounds, such as

are made in extirpation of the axillary and supraclavicular lymph-glands, considerable quantities of lymph may ooze out into the dressings from the cut lymphatics for a day or more ; but this transudation ceases spontaneously. When an opened lymph-vessel remains permanently patent, so that lymph continuously escapes, either externally or into a large cavity, the condition is known as lymphatic fistula.

Wounds of the thoracic duct, as well as rupture in consequence of obstruction, result in large accumulations of lymph either in the peritoneal cavity, giving rise to *chylous ascites*, or in the pleural cavity—*chylous hydrothorax*. Such conditions may be fatal on account of the disturbance of nutrition that follows when the chyle is prevented from entering into the general circulation.

Chyluria signifies escape of chyle with the urine. It occurs after invasion of the lymph-vessels of the abdominal cavity and the thoracic duct by a parasite, the *Filaria Bancrofti* (see page 346), which causes obstruction to the lymph-current and secondary dilatation and rupture of the lymph-vessels in the walls of the urinary bladder.

EDEMA.

The intercellular spaces of the tissues and the serous surfaces are bathed in a clear, watery fluid, or lymph, that passes from the blood through the capillary walls, and is again emptied into the blood by the lymph-vessels and the thoracic duct, a part also being reabsorbed by the veins.

This fluid, or lymph, is the result of diffusion and filtration through the capillary walls. The exact composition, which varies in different parts of the body, is, according to Heidenhain, materially influenced by active secretory processes on the part of the endothelial cells of the capillaries ; but physiologists do not agree that a definite secretory activity of these cells has been proved.

When the amount of transudation from the blood exceeds the absorptive power of the lymphatics, the result is an accumulation of clear, watery fluid in the tissue-spaces, which is termed *edema*, or *dropsy* (*hydrops*).

Accumulation of transudate in the abdominal cavity is known as ascites, in the pleural and pericardial cavities as hydrothorax and hydropericardium, respectively, in the tunica vaginalis as hydrocele, in the spaces of the pia-arachnoid as external hydrocephalus, and in the ventricles of the brain as internal hydrocephalus. A universal edema of the subcutaneous and inter-muscular connective tissue is known as anasarca.

The fluid of edema may be described in general as a clear, usually colorless liquid of low specific gravity, containing a smaller amount of proteids, especially of fibrinogen, than the blood-serum. An inflammatory exudate, on the other hand, is usually turbid, often bloody, of a high specific gravity, and rich in proteids, containing sometimes enough fibrinogen to form fibrin in large quantity.

Formerly the teachings concerning the causation of edema were largely governed by the notion that the transudation occurred through a healthy, unchanged vascular wall, in contradistinction to the inflammatory exudation, which, on account of its more complex composition, was properly regarded as due to grave alterations in the vascular wall. At the present time this distinction between edema and inflammatory exudate, between transudation

and exudation, does not hold good, because there can be no doubt that changes in the walls may play an important part in the formation of certain transudates as well as of exudates.

The formation of the transudates of edema depends principally upon pathologic variations in the blood-pressure, in the composition of the blood, and in the structure and function of the capillary wall.

Experiments have demonstrated that obstruction to the current in the lymph-vessels does not, as a rule, cause edema, on account of the abundant and universal anastomoses, and because the lymph may be reabsorbed by the blood-vessels; total occlusion of all the lymph-vessels of a part may, according to Baldaert, give rise to a pure lymphatic edema, and in the case of increased production of lymph obstruction to the lymph-vessels will hasten the development of edema. Obstruction of the thoracic duct by tumors or other causes usually gives rise to the development of chylous ascites, often preceded by rupture of the receptaculum chyli.

Increased arterial pressure alone does not give rise to edema as long as the venous return is unhindered; but in passive congestion there is an increased transudation from the blood-vessels that often results in the production of edema.

Edema as the result of passive congestion occurs in a widespread almost universal form in cases of general passive hyperemia, such as develops in uncompensated valvular heart disease, in marked cardiac insufficiency from any cause, and as a result of great obstruction to the current through the pulmonary capillaries. In these instances edema usually begins first in the most dependent parts of the body, where the additional influence of gravity causes the greatest increase of the pressure in the veins and capillaries. In general passive congestion the development of dropsy is aided by the fact that on account of the increased intravenous pressure there is some obstruction to the emptying of the large lymph-vessels into the veins at the root of the neck.

Local edema follows local passive hyperemia; thus obstruction to the portal circulation is followed by the development of ascites, except in such occasional instances in which an efficient collateral circulation develops.

The edema is the consequence of the great accumulation of blood in the veins and capillaries, as a result of which the serous fluid is pressed out through the capillary wall into the tissue-spaces to such a degree that the lymphatic circulation, increased to its utmost extent, is not able to remove the excess of transudate. It is reasonable to assume, however, as certain experiments seem to indicate (Emminghaus), that in consequence of long-continued intravascular pressure the permeability of the vessel-wall may be increased. It would seem that under these circumstances the thin, delicate capillary wall could very easily become so altered that liquid would transude more easily than in health. The long-continued distention of the vessels and the consecutive nutritive disturbances may also lead to a loss of elasticity of the extravascular tissues, and this undue laxity would favor the accumulation of lymph.

Increased transudation from the capillaries, with the production of edema, also takes place under a variety of circumstances in which the essential underlying condition seems to be some alteration of the capillary wall. These are the so-called hydremic edemas, which occur more particularly in conditions of chronic infection and nutritive disturbances leading to cachexia. The

edemas now referred to were formerly ascribed to hydremia—*i. e.*, either to an actual increase in the amount of water in the blood, or to a relative increase due to a diminution in the amount of proteids in the serum. But this theory has never been satisfactorily verified by experiment. The injection of large quantities of a 0.6 per cent. solution of salt into the vascular system of animals does not produce edema (Cohnheim and Lichtheim). Even when the blood is replaced to the extent of about one-half its volume by salt solution, so that a marked hypalbuminosis exists, typical edema fails to develop. Still, von Recklinghausen and others hold fast to the hydremic theory. But inasmuch as clinical experience shows that hydremia may exist without dropsy, and that edema may develop without hydremia and without passive congestion, it is quite reasonable to look to anatomic and functional alterations in the capillary walls as the essential causes of certain dropsies.

Hamburger believes that a dropsy of bacterial origin may be produced by bacterial products that circulate in the blood, and either increase the permeability of the capillary wall or stimulate the endothelial cells to an excessive or perverted functional activity. Toxic substances of other origin and the changed composition of the blood in some diseases, such as nephritis, may have similar effects.

Cohnheim and Lichtheim ascribed hydremic edema to a pathologic permeability of the vascular wall. Cohnheim, as well as Thoma, calls attention to one-sided pleuritic effusion, and to unequal amounts of transudation in the two pleural cavities in bilateral hydrothorax (both frequently observed in cases in which the same amount of blood must have been brought to the two pleural membranes under the same general conditions), as pointing directly to a marked difference in the structure and function of the capillary walls in the two sacs. The differences in the case of double hydrothorax may also be due to pressure of the heart itself, particularly the enlarged right auricle, on the return veins.

Heidenhain found that intravascular injection of certain substances, such as the enzymes of the salivary, pancreatic, and gastric secretions, pepsin, egg-albumin, and decoction of the muscles of crabs and crayfish, produced a marked increase in the transudation from the blood—phenomena which he explained as due to the stimulation by these substances of the secreting functions of the endothelial cells.

Recently Loeb has suggested that edema is due to chemical changes, chiefly the result of lack of oxygen, that cause an increase in osmotic pressure in favor of the tissues over the blood and lymph. Pressure thus produced may exceed many times that of obstruction to the circulation.¹

Thoma found that in dead persons arteries and other vessels, the seat of chronic sclerotic changes, were much more permeable to salt solution, injected under a certain pressure, than healthy vessels; and he proposes to call the hydremic edema of cachectic diseases angiosclerotic edema, because there is reason to believe that in a considerable proportion of instances of edema actual vascular disease, or angiosclerosis, is present.

It is a well-known fact that edema is relatively frequent in persons with arteriosclerosis; but the so-called hydremic edema often develops in patients without any arterial or vascular disease in the sense of sclerosis; hence it would perhaps be more in accordance with the actual condition of our

¹ Opitz, *Jour. Am. Med. Assoc.*, Jan. 14, 1899, reviews the development of the theories of edema.

knowledge to refer to this group of edema as angiopathic rather than as angiosclerotic.

The so-called inflammatory edemas probably represent the transition stage between the vascular changes that give rise to pathologic transudation or edema and those that lead to exudation. The fluid of inflammatory edema differs from that of the previous groups in containing more proteids, a larger number of leukocytes, and also fibrinous masses. Inflammatory edema may occur in the vicinity of inflammatory foci, when it is often spoken of as collateral edema; or it may occur as a primary condition, characterized by circumscribed foci of transudation, caused by various toxic, thermic, and traumatic influences, the action of which remains essentially local. Undoubtedly the vascular alterations in these conditions are identical with, or approach very closely, the vascular changes in inflammation that give rise to exudates.

The appearance of edema after spinal paralysis, and the edema of the paralyzed side in hemiplegia, point strongly to the production of an increased permeability of the capillary wall, and excessive transudation or imperfect removal of lymph on account of disturbed vasomotor innervation. Whether so-called neuropathic hyperemias, simple and inflammatory edemas of the skin, as urticaria, erythema nodosum, and angioneurotic edema, as well as those observed in some forms of poisoning and in persons with idiosyncrasy to certain fruits and foods (strawberries, rhubarb, crabs, and shell-fish), are primarily neuropathic or toxic in origin, must be left for future investigators to decide. Wright¹ believes that in some of these conditions a defective coagulability of the blood is produced that leads to transudation. Janowski has shown experimentally that the severing of the vasomotor nerves in conditions associated with edema is followed by marked increase in the transudate.

Transudates in general are colorless or pale yellow, clear fluids, of alkaline reaction, containing a varying amount of proteids, extractives, and salts. A few leukocytes and red blood-corpuscles are also usually present, and in the dropsical accumulations of serous cavities more or less desquamated and degenerated endothelial cells and fat-drops will be found; on rupture of chyle-vessels, chyle may become mixed with the fluid of an existing ascites to such an extent that turbidity results. The milkiness of certain exudates and transudates is, however, not always due to an admixture of chyle, but may depend on a precipitation of albumin.

The composition of transudates is related to that of the blood. Thus, the quantity of proteids and salts in transudates, while always less than that of the blood, corresponds approximately to the amounts of these substances in the plasma (Hoffmann). When the plasma contains certain abnormal substances these may also appear in transudates, as uric acid in nephritis, sugar in diabetes, and biliary coloring-matter in jaundice.

Thoma² gives the following as the specific gravities and percentages of albumin of certain transudates:

	Specific gravity.	Percentage of albumin.
Ascitic fluid in nephritis	1.006	0.56
Ascitic fluid in portal obstruction (cirrhosis of liver)	1.008	0.97
Ascitic fluid in general venous congestion	1.012	1.96
Pleural effusion in nephritis	1.007	
Pleural effusion in general venous congestion	1.012	1.30
Transudates of varying origin	1.007-1.011	0.05-1.1

¹ *Lancet*, ii., 1896.

² *Allg. path. Anat.*

Dropsical organs and tissues present a more or less characteristic waterlogged appearance owing to the accumulation of fluid in the tissue-spaces. Tissues containing many spaces may be greatly swollen; an edematous extremity may swell to many times its normal size, due to the dilatation of all the interstices and spaces by fluid, and the skin may be stretched to its utmost. Under pressure of the finger some of the fluid is squeezed aside, and more or less well-marked "pitting" results, which may persist for some time on account of the diminished elasticity of the tissue. Incision of the skin is followed by the outflow of a clear, watery fluid, and reveals the spongy meshes of the subcutaneous tissue filled with transudate. Edema of the lungs is characterized by an increase in volume and great increase in weight; the alveoli are filled with fluid, which on pressure runs freely from the cut surface; if the edema existed before death, so that air was mixed with the fluid, the latter will be frothy. Solid organs, like the kidney, on section show a moist, glistening surface.

Body-cavities the seat of marked and long-continued dropsy usually become dilated, and the serous lining is often grayish and opaque, owing to loosening and degeneration of endothelial cells. Compressible organs, like the lungs, are rendered more compact by the pressure of the fluid (compression-atelectasis).

The transudates gather first in the intercellular spaces, but may also soak into the tissue-elements, producing vacuolation and softening of cells and fibers (Fig. 6).

The consequences of edema *per se* chiefly depend upon its localization. Thus, edema of the folds and structures about the entrance to the larynx (edema of the glottis) may cause rapid death from asphyxia. Edema of the lungs is also often the immediate cause of death. Dropsical accumulations in the peritoneal and pleural cavities may produce such pressure upon the lungs and upon the diaphragm as to interfere seriously with respiration. An acute transudation into the ventricles of the brain and the pia-arachnoid spaces may cause fatal intracranial pressure.

Edema in general is ominous on account of the grave nature of the processes that underly its development.

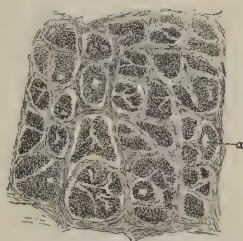


FIG. 6.—Edema of the optic nerve on account of tumor of the cerebellum. At *a* is a vacuole in a nerve-bundle. Weigert's stain. $\times 75$.

THROMBOSIS.¹

Thrombosis is the coagulation of the blood within the heart or blood-vessels during life. The resulting coagulum is known as a thrombus. Masses formed by the adhesion of altered blood-corpuscles and their derivatives are also called thrombi.

The coagulation of blood is a chemical process resulting in the production of fibrin, and it awaits a more simple and satisfactory explanation than it is possible to give at the present time.

The subject is an extremely complex one; it is inseparably connected with the chemistry of the proteids of the blood, and a complete knowledge

¹ For a full and exhaustive consideration of thrombosis and embolism in all their bearings, consult the article by Welch, in Allbutt's *System of Medicine*, vii., 1899.

of coagulation must needs rest upon a better understanding of the nature of these bodies.

Alexander Schmidt,¹ after devoting a lifetime to the study of clotting of the blood, came to the conclusion that the following factors are necessary for the occurrence of the process: 1. Certain soluble proteids, namely, paraglobulin and its derivative, fibrinogen, forming the material from which fibrin is derived. 2. A special ferment, namely, fibrin-ferment, or thrombin, as he calls it, to bring about the necessary changes in the proteids mentioned. 3. A certain amount of neutral salts for the precipitation of the fibrin in an insoluble form.

Arthus and Pages demonstrated conclusively that without the presence of calcium salts fibrin cannot be formed from fibrinogen. They showed that if potassium oxalate is added to freshly drawn blood in such quantity as to precipitate the calcium salts, clotting will be prevented. If a soluble calcium salt is again added, clotting will promptly occur.

In order to explain the relation of the calcium salts to the fibrin-ferment, or thrombin, Pekelherring advances a theory which has been somewhat modified by Lilienfeld, and is based upon the fact that from blood-plasma a nucleo-albumin can be isolated, which, if brought into a solution with fibrinogen and calcium salts, causes a typical clot. The theory is that the so-called "fibrin-ferment" of Schmidt is a compound of nucleo-albumin and calcium, and when it is brought into contact with fibrinogen a reaction takes place, the calcium uniting with parts of the fibrinogen molecule to form an insoluble calcium compound, fibrin. The nucleo-albumin is derived from the leukocytes and blood-plates when they break down and go into solution, and this nucleo-albumin then unites with the calcium salts to form the fibrin-ferment.

Coagulation of the blood depends, then, upon the chemical reaction between fibrinogen of the blood-plasma and the nucleo-albuminate of calcium, in consequence of which an insoluble albuminate of calcium-fibrin is precipitated. Fibrinogen and calcium salts exist in the circulating blood, but the nucleoprotein is derived from the disintegration of the formed elements of the blood, as the leukocytes and the blood-plates. The exact reaction which occurs when fibrin is formed cannot be stated, but it would seem to be quite satisfactorily settled that fibrin is a compound of calcium with a part of the fibrinogen molecule.

It must be assumed that in health thrombosis is prevented from occurring because nucleoproteids are not present in sufficient quantity at any one time. It is true that the necessary elements for fibrin formation are always present, some nucleoproteids being liberated by the constant destruction of blood-corpuscles; but the smoothness of the endothelial lining prevents the violent disintegration of cells in such numbers that enough nucleo-protein is liberated at once to cause the precipitation of fibrin; and probably the small amount of nucleoprotein, or fibrin-ferment, set free under normal conditions is quickly changed or neutralized.

Stagnation of the current favors thrombosis, but does not alone necessarily produce it, because Brücke, Baumgarten, and others found that the blood coagulates with extreme slowness in the lumen of a vessel between two carefully applied aseptic ligatures, continuing fluid for weeks if the vessels are allowed to remain in the living body. A further illustration of the

¹ *Zur Blutlehre*, Leipzig, 1893.

importance of purely physical conditions in the coagulation of the blood is seen in Freund's demonstration that it is possible to maintain the fluidity of the blood for quite a long time by receiving it in sterile glass vessels coated with vaselin, whereas in vessels without any oily coating the blood-corpuscles disintegrate and determine coagulation.

As would be inferred from such observations, thrombosis occurs when the endothelial lining has been roughened or destroyed either by wounds or disease. And yet it is a matter of frequent experience to observe rough and degenerated areas in the endothelium of the vessels, especially of the arteries, without thrombosis. On the other hand, thrombi are found most frequently in those parts of the circulatory system in which the blood-current is liable to become slow and irregular, as in the systemic veins, the recesses connected with the cavities of the heart, in aneurysms, etc. Hence it must be concluded that retardation and irregularities of the current favor thrombosis, not only because of impairment of the nutrition of the endothelium, but also because they seem to be at times associated with or cause changes in the blood-corpuscles that induce the formation of thrombi. According to Freund, the adhesive character of abnormal surfaces is of special importance in causing thrombosis. Irregularities in the current throw the blood-corpuscles more violently against the rough places in the wall, and hence hasten thrombosis in somewhat the same manner as whipping a mass of blood hastens coagulation.

Occasionally instances of unusually rapid and extensive thrombosis are observed that seem to depend upon changes in the general composition of the blood. Such thrombi have been ascribed to so-called ferment-intoxications, and form after extensive injuries, snake-bites, large burns, arsenic poisoning, etc., and in conditions of great general exhaustion. Experimentally it is possible to produce thrombosis by the injection of fluids containing nucleo-albumins; but the fact that thrombosis is somewhat difficult to produce by these methods shows that the body can protect itself within certain limits against coagulation. It is likely that living endothelial cells in some manner restrain coagulation; and Lilienfeld has shown that in connection with leukocytic disintegration a proteid called histon is sometimes formed which has the power to hinder clotting.

Thrombosis may consequently arise under the co-operation of at least three different factors, namely, lesions of the lining of the vessels, irregularities and slowness of the blood-current, and changes in the blood. The two that most frequently enter into the process, and to the direct or indirect concurrence of which the majority of thrombi are attributable, are the lesions of the vascular lining and the disturbances of the blood-current. Zenker has observed that endothelial cells undergoing necrosis present the appearance of a star surrounded by a fibrinous network, showing that the dead endothelium may induce fibrin precipitation, presumably by the formation of the necessary nucleoproteid.

According to their composition, depending upon the relative amount of blood-plates, leukocytes, and red blood-corpuscles, thrombi are usually classified as blood-plate thrombi, and as white, red, and mixed thrombi; between the latter there may be intermediate forms.

The blood-plates (Bizzozero), or hematoblasts (Hayem), are regarded by some as normal constituents of the blood, and by others as the products of the disintegration of white blood-corpuscles (Weigert), or as precipitated globu-

lin (Löwit), or as being formed by the breaking up of red blood-corpuscles (Wlassow, Arnold). Their exact relation to thrombosis has been the subject of much discussion. Bizzozero regarded them as the essential factor in the formation of fibrin, in the sense that they liberated the fibrin-ferment as they underwent destruction; but this conclusion has been questioned by other observers (Weigert, Löwit, Eberth and Schimmelbusch, and others). The so-called blood-plate thrombi have been shown experimentally by Eberth and Schimmelbusch¹ to be formed in conditions of retarded circulation with disturbances of the axial and peripheral currents; if the vessel is compressed or injured chemically with silver nitrate or other agents, a mass of blood-plates will form at the point of injury. At first the individual plates may be recognized, but soon the mass becomes granular or homogeneous. This is the colorless blood-plate thrombus; and upon this may be situated a greater or smaller number of leukocytes. Eberth and Schimmelbusch designate the formation of this thrombus not as coagulation, but as conglutination; and the secondary transformation into a homogeneous or granular, more compact mass, as viscous metamorphosis.

There is much in favor of the theory that the platelet-thrombi are the result of coagulative processes. Löwit, who looks upon the blood-plates as globulin precipitated from the red corpuscles, holds that the plate-thrombus is due to a kind of coagulation, and that the fibrinous substance produced is closely related to the fibrin found in red and mixed thrombi. Arnold and his pupils bring forward strong evidence of a morphologic character to the effect that the separation of platelets from red corpuscles and the formation of fibrinous material from the platelets and other substances derived from the red corpuscles constitute an early and essential step in both intravascular and extravascular coagulation of the blood.

The importance of blood-plate thrombi lies in the fact that they are in all probability the foundation for further and more extensive formations of fibrin and leukocytes that are known as white thrombi.

White thrombi were shown by Zahn to form, like platelet-thrombi, in the marginal zone of the moving stream. In this part of the moving stream red blood-corpuscles are absent. When the wall is injured, or great slowness or gyrations of the current arise, then the marginal zone may become the seat of coagulation. Either a plate-thrombus forms first, fibrin being deposited upon it in successive layers, or a filamentous, fibrinous mass is formed, enclosing blood-plates and white blood-corpuscles. In either case the thrombus, which is coral-like in form, becomes adherent to the vessel-wall, and may grow by apposition of new fibrin until it reaches the axial zone, when red blood-corpuscles become enclosed in the fibrinous network, and the thrombus becomes in part red, in part white—*i. e.*, mixed. From a small beginning, either as a blood-plate thrombus or as a mass of fibrin and leukocytes, the thrombus may grow, by successive deposits of fibrin around its peripheral zone, until it reaches the axial stream and perhaps occludes the vascular lumen. Undoubtedly the majority of the white and mixed thrombi in man originate in the described manner.

The white thrombus is actually gray or yellowish-white in color. Microscopically it consists of minute or coarse threads, that either run irregularly parallel to one another or form a network of granular and hyaline material, and a larger or smaller number of leukocytes and occasional red corpuscles.

¹ *Die Thrombose*, 1888.

The granular and hyaline masses are regarded as due to changes in conglutinated blood-plates, which form a sort of trabecular framework, while the threads are typical fibrin. With time the amount of fibrin increases considerably. The number of leukocytes in the interior of these thrombi is sometimes very great; and as the majority may stain well and appear well preserved, the impression is created that many may have been attracted to the thrombus and wandered into it after it was formed.

Red thrombi occur in stagnating or quiet blood when the conditions are favorable for the precipitation of fibrin. They consist of closely aggregated masses of red cells, separated by delicate or coarse threads of fibrin. Leukocytes are also present.

The mixed thrombus is composed of white and red layers. It may be formed, as already indicated, when a white thrombus gradually extends from its mural attachment out into the current so as to interrupt the axial stream; or it may form by alternating rapid and slow coagulation in larger cavities, as in aneurysms, when the thrombus frequently presents a distinctly laminated appearance. White thrombi may, as they contract, present crevices and cracks into which the blood may pass and clot.

In infective and toxic states capillaries and smaller vessels may be the seat of hyaline thrombi. The hyaline material stains with Weigert's fibrin method, and is regarded by some as derived from red corpuscles, by others as coming from leukocytes.

Thrombosis occurs oftenest in those parts of the circulatory system in which the movement of the blood is subjected to the greatest disturbances, namely, in the systemic veins and in the recesses of the cardiac cavities (the auricular appendages and between the muscular trabeculae of the ventricles). Thrombi are found here in about one-third of those that die from chronic diseases (Birch-Hirschfeld). Wounds, degenerations, and inflammations of the intima of the vessels and of the heart, abrupt dilatations in the course of the vessels, such as aneurysms and varices, narrowing of the vessels from external compression, are all conditions favorable for the development of thrombosis.

Wounds of the blood-vessels usually lead to the conglutination of blood-plates along the margins, and this may be followed by the growth of a white thrombus, the whole being a process which may be of material aid in the immediate closure of the opening.

Ligation of a vessel leads to arrest of the current up to the nearest collateral branch. Baumgarten has shown that a carefully tied ligature need not be followed by thrombosis; but if the intima is ruptured by the unnecessary tightening of the ligature a small thrombus forms along the circular tear. If the vessel is the seat of sclerotic changes with defects in the endothelium, or if acute suppurative inflammation develops, then a red thrombus is sure to form up to or beyond the nearest branch. If the ligature now "cuts through" the wall—*i. e.*, if union between the opposed surfaces fails to occur—the thrombus is the only guard against hemorrhage; it may give way readily, and this would be followed by the dreaded secondary hemorrhage of the preaseptic era.

In the heart the various forms of acute endocarditis are nearly always associated with thrombic deposits upon the necrotic and changed areas, helping to form the vegetations characteristic of endocardial inflammation. Thrombi that originate primarily in the auricular appendages or in the

recesses between the muscular trabeculæ of the ventricles may grow by apposition to form larger masses that formerly were designated as cardiac polypi. Occasionally such polypoid masses become loosened, and if they are too large to pass the auriculoventricular openings, they remain in the auricles as free "ball-thrombi."

In the arteries white or mixed thrombi may develop upon roughened places in the intima and project as *parietal* or *mural* thrombi into the lumen of the vessel (Fig. 7). In a smaller vessel such parietal formations



FIG. 7.—a, Parietal thrombus upon a rough (atheromatous) spot in the intima of the aorta.

may grow by apposition until the lumen becomes completely closed, when the thrombus is spoken of as *occluding*. Such original or *primary* (autochthonous) thrombi may give rise to *secondary* thrombic deposits, that grow chiefly in the direction of the blood-current and extend as far as the nearest branch, and sometimes farther; such secondary, propagated, or induced thrombi are usually red, due to coagulation in the blood-mass.

The dilatations or aneurysms that develop in connection with arteries are frequently the seat of extensive thrombosis—dilatation-thrombi—because of the roughness of the intima and the whirls and eddies made by the blood-current in their interior.

In the veins varicosities, as well as interferences with the venous circulation in general, may give rise to small white thrombi in the pockets formed by the valves; these primary thrombi may grow by surface deposition until they occlude the lumen and give rise to a propagated red thrombus reaching to the next branch. Here the projecting blunt end of the thrombus may become capped by white or mixed deposits until the lumen is once more closed; a new red thrombus again forms, and this process may repeat itself until the small primary thrombus behind the valve of a vein—in the leg, for instance—may have given rise to thrombosis far up into the vena cava.

Suppuration and necrosis in the vicinity of veins or arteries which extend so as to involve the vascular wall, or inflammation and necrosis due to the implantation upon the intima of micro-organisms circulating in the blood, or to the action of toxic substances, also frequently give rise to thrombosis; and in this case the thrombus is often invaded by bacteria (suppurative thrombophlebitis or thrombo-arteritis). Thrombosis of the smallest vessels is frequently caused by infectious or toxic inflammations and necrosis in the tissues around them (Fig. 8).

The general states especially favorable to the development of thrombosis

are those marked by great prostration and cardiac feebleness. Thrombi developing under these conditions are commonly called *marantic* thrombi, according to Virchow, who regarded the marasmus as the underlying factor.

Thrombi of this class are found in the pockets of the valves, in the auricular appendices, in the recesses between the muscular trabeculae of the cavities of the heart, but most frequently in the sinuses of the dura mater and in the femoral veins; here extensive thrombosis may take place. The general weakness of the heart, the slowness of the circulation, and the vitiated condition of the blood in marasmus all favor local degeneration of the endothelium. In many instances of marantic thrombosis it is difficult to exclude entirely the influences of accidental or terminal infections.



FIG. 8.—Small tubercle with giant cell in the wall of a pial vein in tuberculous meningitis, covered with a hyaline granular thrombus containing many leukocytes. Alcohol, paraffin, hematoxylin, and eosin. $\times 150$.

The extensive thrombosis that at times follows injection of extract of thymus gland, and the transfusion of blood from one animal into one of another species, sublimate and arsenic poisoning, and many general infections, makes it probable that chemical substances may gain entrance to the circulation and determine thrombosis by their direct action upon the constituents of the blood (ferment-thrombosis).

Disturbances of the circulation and changes in the vessel-walls determine the localization of thrombi; while changes in the chemistry and morphology of the blood are important predisposing causes (Welch).

The principal causes of thrombus formation may, following Birch-Hirschfeld, be summarized in this way:

1. *Thrombosis from adhesion*: a. On foreign bodies; b. On the inner surfaces of vessels the seat of necrosis, fatty degeneration, or inflammation.
2. *Thrombosis from stagnation*: a. From local disturbance from ligation, compression, circumscribed dilatation; b. From general circulatory weakness (marantic thrombosis).
3. *Thrombosis from fermentation*: a. Due to destruction of blood-corpuscles; b. Due to the introduction of ferments formed outside of the vessels.

The immediate consequences of thrombosis depend upon the character of the thrombus, whether it is parietal or occluding, and upon the vessel involved, whether that is provided with collateral branches or not. An occluding venous thrombus causes passive congestion and increased transudation in case collateral circulation does not develop, as, for instance, in the portal vein. An occluding arterial thrombus has, in general, the same effects as embolic arterial occlusion.

The more indirect results of thrombosis are connected with the secondary changes that take place in thrombi. A thrombus retains its original structure for a very brief time only. The changes that occur may be separated into five principal kinds: hyaline and granular transformation, substitution with connective tissue, calcification, simple softening, and septic disintegration.

It must be mentioned that a fresh or recent thrombus may be detached, either in part or as a whole, and carried farther in the current as an embolus

until it becomes impacted in some vessel the lumen of which is too small to allow its passage. The farther changes of such an embolus are essentially the same as would have occurred if it had remained as a thrombus at its place of formation.

The hyaline-granular transformation begins with a contraction of the fibrin in the thrombus, which squeezes out the fluid in its interior and reduces its size. The fibrin and red and white cells undergo disintegration into a granular mass, which later may become homogeneous. The columns of platelets are recognized with difficulty. The hemoglobin is transformed into various pigments, and is in part removed. Gradually the mass shrinks still more, becomes quite dry and rather firm. This contraction of the thrombus may reopen the lumen in case it was occluded. Such a hard, hyaline and granular thrombus may now be gradually replaced by connective tissue. In this process the thrombus, which must be regarded as an absolutely dead mass, does not take an active part. The new connective tissue comes entirely from the vessel-wall. In the interior of the thrombus leukocytes appear that have wandered in from the blood, and act as phagocytes. Beginning at its points of attachment to the wall, a layer of endothelial cells gradually spreads over its surface. Simultaneously new capillaries spring from the vasa vasorum and enter the thrombus. The endothelium on the surface of the thrombus also forms vascular spaces. New connective tissue develops around the capillary loops. This connective tissue comes from proliferation of cells in the wall of the vessel (or heart). The capillaries from the vasa vasorum unite to a certain extent with the spaces formed by the endothelial cells; the thrombus is now vascularized, and communication may be established with the lumen of the vessel. Gradually the thrombus becomes smaller, due to contraction of the newly formed connective tissue and to absorption of the dead material. Finally the absorption may be complete and the contraction so extreme that merely a narrow strand of fibrous tissue marks the site of the former clot, and the blood-current passes unhindered; or there may remain more or less distortion or narrowing of the lumen and thickening of the wall. In unfavorable instances, especially when the thrombus remains attached for some part of its extent to the entire circumference of the vessel, the latter may become converted into a fibrous cord without any lumen whatever in its interior.

For various reasons a thrombus may fail to become replaced by connective tissue. Disease of the vessel-wall and infection may prevent or delay the process. In the old the changes require a longer time than in the young.

Thrombi may become impregnated with the salts of lime and calcify. This may occur in thrombi upon the valves of the heart as well as in those in the interior of vessels. The concretions formed are spoken of as phleboliths in the case of veins, and as arterioliths in the case of arteries. Phleboliths are the more common, and are found quite often in the venous plexuses in the pelvis.

While connective-tissue substitution and calcification are favorable terminations of thrombosis, the forms of softening that occur in thrombi are connected with grave dangers.

Simple, or bland, softening is the result of obscure chemical or fermentative changes in the interior of the thrombus without the presence

of bacteria. The center is gradually changed into a soft, reddish-gray or grayish detritus; if the softening extends to the superficial layers of the thrombus, then the particles and fragments may be discharged into the circulation and give rise to embolism.

Septic, or purulent, softening of a thrombus is due to the presence of micro-organisms, and occurs especially when the thrombus develops in connection with suppurative phlebitis or arteritis, although infection may occur in a thrombus formed upon sterile walls. There is an accumulation of polynuclear leukocytes, and the thrombus is changed into a yellowish, purulent fluid, which may become putrid and foul. If the infected material is transported by the current to distant places, secondary foci of suppuration and the condition known as pyemia may develop.

After death the blood recedes to the capillaries, the veins, and the heart by the retraction of the arteries. Probably because in contact with endothelium it remains liquid for some little time, but within a few hours it clots. When this coagulation is rapid the coagula are dark red. If it is slow, variations in color may appear. The red blood-corpuscles, being specifically heavier, sink before coagulation begins, and the uppermost plasmatic layers form yellow fibrinous clots (chicken-fat clots) which are moist and gelatinous, while the lower strata consist of deep-red masses (currant-jelly clots). The agonal and postmortem clots are not stratified; they are moist and gelatinous, not granular; and they are not intimately attached to the vessel-wall or heart-wall, although they may be infiltrated between the muscular trabeculæ of the cavities of the heart.

EMBOLISM.

Our knowledge of embolism rests essentially upon the anatomic and experimental investigations and teachings of Virchow.¹

Embolism is the impaction in some part of the vascular system of any undissolved material brought there by the blood-current (Welch). The material transported in this manner is an *embolus*.

A systematic consideration of embolism necessitates a brief account of the origin and nature of the various kinds of emboli, of the routes of transportation and the manner of lodgement, and of the mechanic as well as the specific results of embolism.

Emboli may consist of:

1. Thrombi or pieces thereof, tissue-fragments, and various kinds of parenchymatous cells.

Many emboli consist of thrombic masses. Either a whole thrombus is loosened from its place of origin or a portion projecting into the blood-current is broken off, or fragments are carried away by the circulation from thrombi that are undergoing either simple or septic softening.

The favorite seats of thrombi that give rise to embolism are upon the endocardium, in the veins of the lower extremities and of the broad ligaments, and in the aorta when the intima is rough and irregular from chronic disease; but thrombi in any part of the circulatory system may become the source of emboli.

Fat-drops constitute the most frequent form of emboli. Fractures with destruction of the bone-marrow, contusions of the subcutaneous adipose

¹ *Gesammelte Abhand.*, 1856.

tissue, acute as well as chronic osteomyelitis, injury to fat-tissue in any part, such as lacerations of the liver, fatty changes in thrombi and in the vascular lining, are all conditions that may be followed by fat-embolism (Fig. 9).

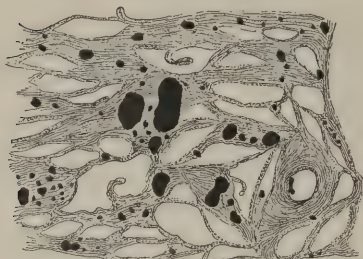


FIG. 9.—Fat-embolism of the lung after fracture of the femur. The fat-globules and masses, stained black with osmic acid, lie in the capillaries of the lung. $\times 150$.

A limited fat-embolism occurs, in all probability, in most fractures, but only occasionally are the results so serious as to attract attention. It also may follow orthopedic interventions. In all these instances the injury, or the disease, causes a disintegration of the cells containing the fat, which then finds its way in larger and smaller drops and masses into the patent lumen of torn veins; occasionally single fat-cells or islands of them may be carried away.

In diseases of the endocardium and of the intima of the blood-vessels degenerated endothelial cells, fragments of the heart-valves, inflammatory vegetations, and calcareous masses may be carried off by the blood-current.

Liver-cells, placental cells, giant cells from bone-marrow, and other parenchymatous cells may form emboli. Embolism from liver-cells (Turner, Schmorl, and others) may follow rupture, acute degeneration, and hemorrhages in the liver. Embolism of placental giant cells (syncytium) and of chorionic villi occurs especially in puerperal eclampsia; but also in normal labor. After injury to bones, in various toxic and infectious conditions, and in leukemia the giant cells of the bone-marrow frequently lodge as emboli in the pulmonary capillaries (Lubarsch, Aschoff, and others). Splenic cells (Welch) and fragments of the myocardium (Charrin and Levaditi) are other examples of cellular emboli. For references to the literature bearing upon embolism of parenchymatous cells, see Lubarsch and Ostertag's *Ergebnisse*.

In most cases cellular emboli undergo retrogressive changes and disappear. It is possible that emboli of apparently normal syncytium may give rise to tumor-growth (Schmorl). Thrombi may form around cellular emboli; this is especially so in regard to liver-cells.

2. Tumor-cells. Emboli composed of living cells, capable of farther proliferation, occur in connection with malignant tumors. In carcinoma and sarcoma isolated tumor-cells or cell-groups may reach the blood-current either indirectly through the lymphatics, or directly when the tumor in its growth penetrates the wall and projects into the lumen of a blood-vessel. On lodgement the cells proliferate and give rise to secondary tumors (Fig. 10).

3. Animal and vegetable parasites.

Bacteria of various kinds, as well as protozoa and the embryos of a few large animal parasites, may be transported by the circulation and act as emboli.

4. Foreign bodies; air.

Foreign bodies rarely, if ever, get into the circulation and act as emboli, except when introduced for experimental purposes; but atmospheric air gives rise to embolism by gaining entrance into veins opened accidentally or during surgical operations. The danger of air-embolism is especially

great when large veins near the thorax are opened, into which the air may be directly aspirated by the negative venous pressure during inspiration.¹

As a general rule, emboli follow the direction of the blood-current. The extent of their travels is largely dependent upon their size. Lodgement takes place in the nearest vessel, the lumen of which is too small to allow the embolus to pass; more rarely an embolus is arrested at an arterial bifurcation.

As the majority of large emboli originate from thrombi in large veins, their natural course is through the right heart and into the branches of the pulmonary artery; emboli originating in the right auricle or ventricle also pass into the pulmonary artery. Here the embolus lodges at some point of narrowing of the artery, usually at a bifurcation, producing closure of the lumen of one or both branches. A friable embolus, composed of an old thrombic mass, may break into many fragments as it strikes the point of the arterial bifurcation; multiple embolism of the smaller branches may thus result. Occasionally the main stem of the pulmonary artery, or its large branches, are completely blocked by an embolus originating in a peripheral vein the seat of an extensive thrombosis. The blocking of the

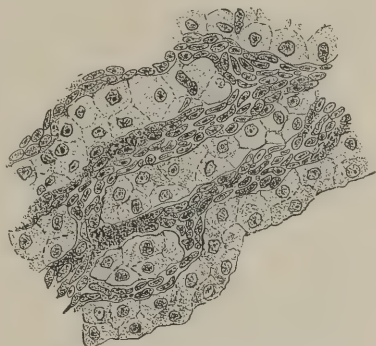


FIG. 10.—Embolism of pigmented sarcoma-cells into capillaries of the liver. The intrahepatic capillaries are filled to distention with spindle-shaped cells containing brown, granular pigment. The liver was uniformly brownish-black, and enlarged to many times its normal size on account of this diffuse infiltration with tumor-cells. The primary tumor was a melanosisarcoma of the eye. Müller's fluid, celloidin, hematoxylin, and eosin. $\times 2500$.

pulmonary artery depends upon the embolus having been rolled together into a large clump by the blood-current; when disentangled by gently moving the embolus to and fro in water, a complete cast of the lumen of the venous network whence it came may be obtained.

Emboli originating in the pulmonary veins, the left ventricle and the left auricle, and the aorta are carried along the arterial current into the more or less distal ramifications of the aorta.

Emboli arising in the radicles of the portal vein lodge in the hepatic branches of this vein—i. e., in the liver.

There are two exceptions to the general statement that emboli follow the normal direction of the blood-current, namely, the case of *paradoxical* or *crossed* embolism, and the case of *retrograde* embolism.

Paradoxical, or crossed, embolism was first described by Cohnheim. It occurs when defects in the interauricular or interventricular wall of the heart, as, for instance, a patent foramen ovale or a congenital defect in the ventricular septum, allow emboli originating in the systemic veins to pass directly from the right chambers of the heart into the left, and to lodge in the systemic arteries instead of in the pulmonary. The frequency with which a patent foramen ovale is seen suggests that crossed embolism is more common than is generally supposed. In cases of obscure systemic embolism this route should be carefully examined. Paradoxical embolism may also take place through the patent ductus arteriosus.

¹ N. Senn, *Experimental Surgery*, 1888.

Retrograde embolism (Heller,¹ von Recklinghausen²) takes place when an embolus is transported in a direction opposite to that of the normal current. As far as we know, retrograde embolism occurs only in the veins; thus, for instance, an embolus may be carried from the ascending vena cava into the renal vein or into the hepatic vein. Cases are described in which tumor-masses and parenchymatous cell-emboli have travelled in a backward direction in the veins. Retrograde embolism is usually explained as caused by sudden reversals in the venous current on account of obstruction to the emptying of the veins into the right auricle, such as great respiratory efforts, etc. Ribbert,³ however, concludes that the emboli which seem to adhere or lie in apposition to the vessel-walls are forced backward slightly with each pulse-beat.

Embolism also occurs in the lymph-vessels; an apparently backward embolism is more frequent here than in the veins, as shown, for instance, by the formation of secondary carcinomatous growths in lymph-glands located behind or distal to primary tumors. Waldeyer and Cohnheim thought the tumor-cells might go in this direction by their own movement. Heller and Vierth⁴ conclude that as lymph-glands become occluded the stream, which is normally very slow, may become reversed; dilatation of the vessels, leading to incompetency of the valves, results, and now backward embolism can easily take place.

Minute foreign masses that can pass through capillary networks are sometimes called capillary emboli; they do not remain indefinitely in the circulatory system, but become deposited in various organs. Arnold found that small foreign bodies in the blood became surrounded and isolated by leukocytes. Numerous experiments by Ponfick and others with granular coloring-matter have shown that it is deposited either free or within cells in various organs, especially the liver, spleen, bone-marrow, and tonsils.

The Effects of Embolism.—The effects of embolism are, generally speaking, twofold: mechanic, depending upon vascular occlusion at the point of lodgement; and specific, depending upon the nature of the embolus, whether infected or sterile, whether composed of dead cells or of living cells capable of further proliferation.

In some instances embolism is followed by sudden death: thus, the closure of the pulmonary artery or its two branches by large embolic masses results in almost instantaneous death; embolic occlusion of the bulbar arteries and of the coronary arteries may cause sudden death.

A moderate amount of fat-embolism can occur without serious consequences; in such cases the fat is gradually saponified and removed by wandering cells. When a large quantity of fat is taken into the circulation it may accumulate in the pulmonary capillaries (Fig. 9); some of it may pass through and lodge in the capillaries of the myocardium and brain, and in the glomerular and intertubular capillaries of the kidneys. Under these circumstances death may occur.

Air-embolism may cause sudden death. When large quantities of air are taken into the circulation, the branches of the pulmonary arteries are filled with bubbles; at the same time there is formed in the heart a frothy mass of blood mixed with air, which is resilient, so that the contractions of the heart are unable to drive it onward. In consequence the left heart

¹ *Arch. für klin. Med.*, viii., 1870.

² *Centralb. für allg. Path. u. path. Anat.*, viii., 1897.

³ *Virchow's Archiv*, c., 1885.

⁴ *Ziegler's Beiträge*, xviii., 1895.

receives but little blood, the aortic pressure falls, and death results. Air-bubbles may also find their way into the capillaries of the systemic circulation and occlude important capillary areas in the brain and in the heart-muscle. The discovery by Welch and Nuttall¹ of *Bacillus capsulatus aërogenes*, which causes an abundant and rapid development of gas in the blood after death, makes it not improbable that some cases of supposed air-embolism were in reality of bacterial nature. Great care must be exercised in the interpretation of obscure instances of death under circumstances that simulate air-embolism, especially when of uterine origin. Experiments show that a much greater quantity of air is necessary to kill animals than can possibly be introduced during an operation. Man, however, seems more susceptible than the dog or the horse.

The changes in the embolus itself after it has become wedged in a vessel depend upon its nature. If composed of sterile thrombic masses, the further changes are those that occur in a sterile thrombus in any part of the circulation. Immediately after the lodgement some new deposits of fibrin may take place upon the surface of the embolus, and the secondary thrombosis may complete the obstruction of the vessel. At the point of impaction necrosis of the endothelium may occur from pressure, followed by connective-tissue proliferation from the vessel-wall and replacement of the mass with granulation-tissue. Occasionally connective-tissue substitution of an embolus leads to obliteration of the lumen of the vessel; at other times the intima presents as a result irregular thickenings or perhaps a more or less elaborate network of connective-tissue threads.

It has been suggested by some that the embolic lodgement of calcareous particles may result in aneurysm and rupture of the vessel in which the embolus lodges.

Emboli composed of aseptic material are called bland, and their effects are only of a mechanical nature, and due primarily to the plugging of the vascular lumen (Fig. 11). As a general rule, occlusion of an artery leads to the development of a collateral circulation, which provides the area nourished by the plugged vessel with sufficient blood-supply. In certain parts of the body, however, the facilities for the development of a collateral circula-



FIG. 11.—At *a* a large embolus is lodged at the beginning of the right common iliac artery, which is occluded by a secondary thrombus, causing gangrene of the corresponding extremity and necessitating amputation. The embolus was a clot from a heart-valve the seat of extensive inflammation.

¹ *Johns Hopkins Hosp. Bull.*, iii., 1892.

tion are either entirely absent or so limited that arterial occlusion is followed by death of the tissue before a collateral circulation has time to develop (page 46). Embolic occlusion of a terminal artery renders the area supplied by that artery primarily anemic. In the spleen, the kidneys, the myocardium, the retina, and the basal ganglia of the brain, arterial occlusion is regularly followed by death of the tissue affected. In the superior mesenteric artery and the pulmonary arteries occlusion, embolic or otherwise, is often followed by necrosis. The further fate of the anemic areas and the special conditions presented after arterial occlusion in various organs provided with end-arteries have been dwelt upon in connection with local anemia and necrosis.

Bland embolism of the branches of the portal vein in the liver is generally without result on account of the additional circulation in this organ provided by the hepatic artery, which normally is abundantly able to maintain the nutrition. When the flow in the hepatic artery is feeble, plugging of the portal branches produces wedge-shaped areas of a reddish color.¹

Peculiarities of embolism of other special vessels are discussed in sections on pathologic anatomy.

Retrograde bland embolism of veins without collateral circulation, such as the splenic and renal veins, causes obstruction to the venous current, extensive passive congestion with perhaps complete stasis, and hemorrhagic infiltration in the areas drained by the occluded veins.

Emboli composed of or containing virulent pathogenic bacteria, animal parasites, or living tumor-cells, may produce on lodgement the same mechanic effects as bland emboli; but these effects usually remain in the background, because the consecutive tissue-changes and new foci of disease caused by the infected and specific emboli are of much greater importance.

Bland capillary emboli are ordinarily of but little consequence, except when in great number; but capillary emboli of virulent bacteria and of tumor-cells are as important as larger emboli, for the reason that when implanted upon the capillary wall of some internal organ, such as the liver, the spleen, the bone-marrow, or the lungs, they give rise to new foci of morbid processes. Thus, for instance, in acute ulcerative endocarditis bits of vegetations and disintegrated tissue containing bacteria may be carried as emboli to the various parts of the systemic circulation, where the bacteria may proliferate and cause multiple abscesses and areas of necrosis. A vein the seat of a suppurative inflammation in its wall, accompanied by thrombosis, may become the source of multiple emboli, large as well as capillary, which, lodging in the lungs and elsewhere, give rise to multiple secondary abscesses. The destructive action of bacteria in emboli may cause such weakening of the vessel-wall at the point of arrest of the embolus that aneurysms develop (embolic or mycotic aneurysms).

Emboli of tumor-cells give rise to multiple secondary tumors in various parts of the body, especially in the lungs and the liver (Fig. 10). In these cases the secondary foci of disease invariably correspond in their kind with the primary focus in which the embolus took its origin.

Secondary embolic foci of suppuration and of malignant tumors are also called *metastatic*; the transplantation by embolism of suppurative infection, as in pyemia, and of malignant neoplasms is known as metastasis.

¹ Chiari, *Centralb. für allg. Path. u. path. Anat.*, ix., 1898.

THE RETROGRESSIVE METAMORPHOSES.

Introduction.—Cellular life and activity are manifested by nutrition, by reproduction, and by function (Virchow). Nutrition is shown by the growth of the cell-body and by the secretion of intercellular substance. Reproduction manifests itself in the phenomena of cell-multiplication. The function of the cell is the office it fills in the service of the organism as a whole.

Nutrition, reproduction, and function are the result of metabolic processes in the cell which transform the energy stored in food into other forms of energy.

As a consequence of disturbances in the activity of the cells there result, on the one hand, different varieties of disintegration and shrinking of the tissues—retrogressive changes; and on the other hand, abnormal forms of growth and proliferation—progressive changes.

The retrogressive changes or metamorphoses depend upon various causes that may operate in different ways. The life of the cell may be directly destroyed by certain agencies, or various degrees of disturbance in the conditions that are requisite for cellular activity and life may arise. In all cases the final result may be the same—namely, cellular death.

When the death of a cell or group of cells occurs directly and rapidly, without the previous intervention of abnormal alterations in the cellular structure, the term *necrosis* is applied. When death of the cell is preceded by a gradual shrinking in size (atrophy), or by demonstrable alterations in structure, due either to abnormal chemical processes in its interior (degeneration), or to the deposition in its protoplasm of foreign substances from without (infiltration), the condition is spoken of as *necrobiosis*.

While the logical distinction between these two general forms of cell-death is easy, it is not always practically possible to distinguish between them on the basis of chemical changes and morphologic appearances. Generally speaking, however, the retrogressive changes that lead to necrobiosis occur so gradually, and present in many instances such definite forms and characteristics, that they are, as a rule, accorded a separate consideration.

As already indicated, under certain circumstances the general environment of the cells is unfavorable in such a way that the consequent imperfect cellular nutrition leads to a progressive shrinking of the individual cells, and this shrinking is designated as atrophy; and necrobiosis is often the further result of atrophy. When abnormal intracellular metabolism converts the cell-protoplasm directly or indirectly into useless and abnormal substances the process is known as *degeneration*, which becomes a necrobiotic change when it leads to the destruction of cells. According to the nature of the substances produced, various forms of degeneration have been established, such as fatty, mucoid, hyaline, etc. When substances produced within the body or introduced into the organism from without are deposited in the interior of cells, which remain essentially passive, or in dead material, *infiltration* is said to occur. Infiltration may reduce the vitality of the cells and thus favor cell-death.

NECROSIS.

Necrosis is the death of individual cells or groups of cells while they are still a part of the living body. Local death preceded by retrogressive changes

in the cells, such as occur in atrophy, in degenerations, and in infiltrations, sometimes receives the special designation of *neerobiosis*.

The real nature and essence of necrosis cannot be expressed in words, since it is not known what constitutes the life of the cell. No one has seen under the microscope, or isolated chemically, the particular detail or substance of the living cell that disappears or changes at the moment of death, and the disappearance or change of which constitutes death of the cell. All those peculiar appearances which indicate that a group of cells was dead while still in the living body or before the surrounding cells died are chiefly postnecrotic or postmortem changes. By means of modern fixing solutions, such as corrosive-sublimate solution, Flemming's solution, absolute alcohol, etc., it is now possible definitely to fix and preserve in the cells the histologic appearances that are present at the moment the tissue is placed in the fluids. Our notions concerning the structure of the normal living cell have largely been gained by studying cells killed in this way.

In necrotic cells the nucleus very soon becomes indistinct, due either to an apparent solution of the chromatic substance, known as *karyolysis* or *chromatolysis*, or to a breaking up of the nucleus into a number of irregular fragments, a form of disintegration which Klebs¹ called *karyorhexis*, and which Schmaus and Albrecht² have shown is initiated by a peculiar transposition of the chromatic filaments. At times the nucleus together with the cell-body changes into a hyaline mass. The cytoplasm of necrotic cells loses its normal granulations and undergoes hyaline transformation, or vacuolation. The exact chemical processes that underlie these changes in necrosis are not known. In many instances the factors necessary for the precipitation of fibrin are present, giving rise to the so-called *coagulation-necrosis*.

The postnecrotic changes vary greatly according to the different conditions surrounding the necrotic part. They serve not only as an evidence that necrosis has occurred, but also, in part at least, as a basis for the classification of the necroses. The secondary vital changes, such as leukocytic emigration and proliferation of the fixed cells occurring about the foci, help to differentiate true necrosis from focal changes that may occur after the death of the organism as a whole.

Necrosis may result from the direct action upon the cells of chemical and toxic substances of various kinds; mechanic insults may also cause direct cell-death; anemia, in consequence of arterial occlusion by thrombosis, embolism, spastic contraction, and compression, is a frequent and important cause of necrosis; complete stasis due to mechanic, chemical, thermal, and trophic injuries of the vessel-wall is likewise often a factor in cell-death. And, finally, disturbances of the trophic and vasomotor innervation may, especially when associated with other causes, produce necrosis. In many instances these agents bring about necrosis at the point of greatest or longest contact; whereas at the periphery more complex reactive tissue and vascular changes are initiated, which are further discussed under Inflammation.

The etiologic and anatomic varieties of necrosis, although not always sharply distinguishable from one another, are best considered under the following subdivisions:

Focal Necrosis.—Focal necrosis occurs in various organs of the body in the course of different infections and intoxications, and is caused by the

¹ *Die krankhaften Störungen des menschlichen Körpers*, 1889.

² *Virchow's Archiv*, 138, Supplement Heft.

circulation in the blood of either living bacteria or of soluble poisons that act more or less directly upon the cells, often without preceding circulatory disorder. In such conditions we find scattered throughout the lymph-glands and parenchymatous organs foci of cell-death, usually microscopic, characterized by certain well-marked changes, of which the most striking affect the nucleus.

Very frequently, perhaps in the majority of cases, the nucleus undergoes fragmentation (karyorhexis, Klebs)—*i. e.*, the chromatin disintegrates into a number of particles and granules, which are scattered about through the focus before they gradually vanish. In other cases the nucleus loses its power of staining with the various nuclear dyes, because the chromatin has been dissolved (karyolysis). At the same time the cell-body becomes homogeneous and opaque, or hyaline, and soon the outlines become completely lost in the granular detritus or the more reticulated material that finally forms. The necrotic material often resembles fibrin.

Attracted by certain substances in the necrotic areas (positive chemotaxis), leukocytes accumulate at the periphery; some of these in turn also die, and suffer nuclear fragmentation and other changes, so that often large quantities of nuclear detritus collect around the areas of cell-death. Later, the necrotic material and detritus become absorbed; regeneration of the dead cells may, in the case of smaller foci, take place by multiplication of the surrounding cells, or the necrotic area may be replaced by newly formed connective-tissue.

Such focal, or insular, necrosis is seen in the lymph-glands, the liver, the spleen, and elsewhere, and was first observed by Oertel in diphtheria. It occurs in experimental diphtheria after subcutaneous injection of virulent cultures of diphtheria-bacilli, and after the injection of the toxins produced by the diphtheria-bacillus (Welch and Flexner).

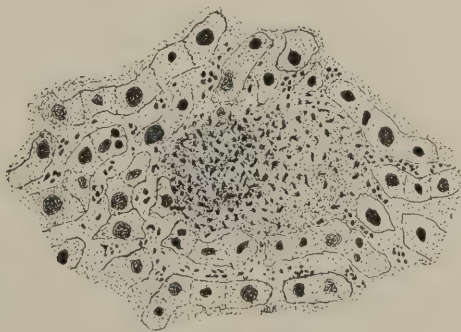


FIG. 12.—Focal necrosis in the liver in puerperal eclampsia. Nuclear fragments are strewn over the necrotic area. $\times 250$.

It is also of common occurrence in typhoid fever. The so-called lymphoid nodules of this disease in the liver and kidneys have recently been shown by Reed¹ to be areas of necrosis; but he was not able to determine whether they were due to the immediate presence of the typhoid bacilli or to the action of the toxins. According to Mallory,² the degeneration of the intravascular phagocytic cells in typhoid fever induces the for-

¹ *Am. Jour. Med. Sci.*, 1895.

² *Jour. Exper. Med.*, iii., 1898.

mation of fibrin, which leads to necrosis. Similar changes occur in scarlet fever (Pearce).

Localized areas of cell-death occur in the liver in puerperal eclampsia (Fig. 12), and also in the spleen, the liver, and the adrenals, in general tuberculosis (Fig. 13) associated with marasmus, in which they have been

shown by Le Cout¹ to be due, in all probability, to the immediate presence of tubercle-bacilli, and not to primary vascular changes.

Focal necrosis in the various organs is regularly produced to a marked extent in experimental intoxication with ricin and abrin, toxalbumins of vegetable origin, and with the toxic substances contained in the serum of the dog's blood (Flexner).² The toxemia of burns also causes areas of necrosis in the organs (Bardeen).

Regarding the causation of focal necrosis in the various conditions mentioned, it would appear that it either results in consequence of the direct action of bacteria, or perhaps more frequently is caused by certain soluble substances, generally known as toxalbumins.

When such soluble toxic substances gain entrance into the circulation, as from a point of local infection, they may, on account of the momentary arrest of the circulation in a capillary, find an opportunity to produce necrotic changes in the capillary wall. Through this altered wall a free transudation of serum takes place, and leads to the death of cells. In other instances the necrosis may result from capillary thrombosis. Necroses may also be produced during the process of elimination or destruction of bacteria or their products by various organs.

The exact genesis of focal necrosis and the further fate of the affected areas are of great interest. It is not unlikely that necroses of this character bear an essential relationship to the production of the connective-tissue overgrowth in certain diseases, as chronic interstitial nephritis and cirrhosis of the liver.

Fat-necrosis.—Fat-necrosis occurs in adipose tissue in the form of yellowish-white, slightly raised, opaque areas of variable size, and usually of more or less circular outline (Fig. 14). Microscopically the contents of the fat-cells are changed into a granular detritus (Fig. 15) or present the appearance of fine needles radiating from the center, while the cells proper undergo necrosis. If the tissue is treated with osmic-acid solution, the surrounding fat-cells stain black, while the necrotic areas remain unchanged.

Langerhans has shown that the detritus in the fat-cells consists of a combination of lime salts with fatty acids.

Fat-necrosis occurs frequently in the abdominal fat in connection with inflammatory conditions of the pancreas. Balser, who first described it, believed that it was due to an overgrowth of fatty tissue, parts becoming

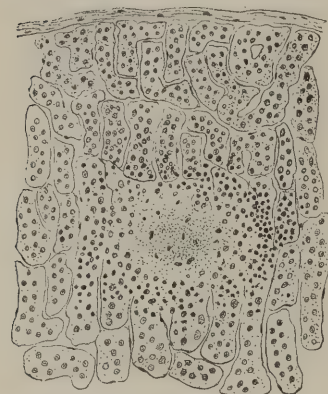


FIG. 13.—Focal necrosis in the adrenal in chronic pulmonary tuberculosis. Leukocytes are accumulating around the area. $\times 150$.

¹ *Jour. Exper. Med.*, ii., 1897.

² *Johns Hopkins Hosp. Rep.*, vi., 1897.

necrotic from lack of nourishment, and held that the pancreatic disease was secondary. Fitz,¹ while concluding from his researches concerning acute pancreatitis that fat-necrosis may occur without any direct relation to pancreatic disease, thought that it often develops secondarily to acute pancreatitis.

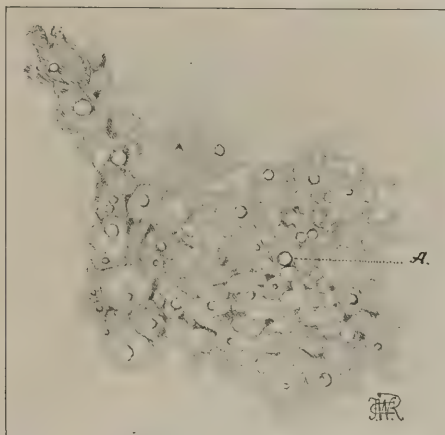


FIG. 14.—Section of omentum with areas of fat-necrosis scattered through it (A). From a case of acute pancreatitis.

It has not been shown that bacterial infection is the cause of this necrotic change in fat, although Ponfick claimed to have found a bacillus in the diseased areas.

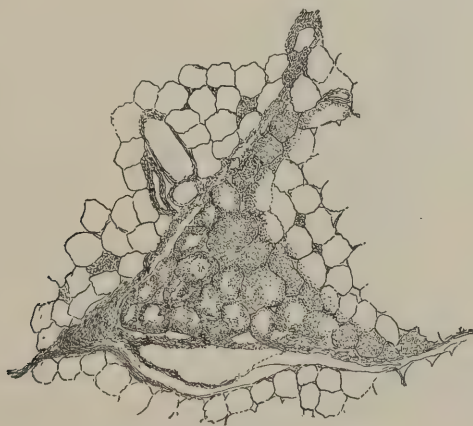


FIG. 15.—Fat-necrosis in the omentum in acute pancreatitis. $\times 76$. The contents of the fat-cells are changed into a granular detritus.

The most plausible theory concerning the cause of fat-necrosis is that it is due to the escape of the fat-splitting ferment of the pancreas, the resulting fatty acids combining with lime salts. Indeed, Langerhans, who first advanced this view, was able to produce fat-necrosis in the subcutaneous fat

¹ *Boston Med. and Surg. Jour.*, xxxv., 1889.

of a dog by the injection of pancreatic extract; and Hildebrand observed fat-necrosis in the pancreas, omentum, and mesentery after deligating all the vessels of the splenic end of the pancreas, which he tied off so as to hinder absorption of the secretion by the blood-paths. Fat-necrosis was also obtained by placing pieces of the pancreas of one animal into the peritoneal cavity of another. Similar results were obtained by Williams. Flexner¹ finally isolated the fat-splitting ferment from areas of fat-necrosis, and produced fat-necrosis by introducing steapsin into adipose tissue.

Necrosis with Gangrene.—Gangrene is a term applied to certain peculiar changes taking place in dead parts. It appears in two forms, as dry gangrene, or mummification, and as moist gangrene.

Dry gangrene occurs in superficial parts of the body which are freely exposed to the air, so that the fluids in the dead tissues evaporate rapidly, the dryness rendering infection with saprophytic bacteria difficult or impos-

sible. The classic example of dry gangrene is the senile gangrene of the extremities, which usually depends upon necrosis due to anemia; here the tissues become dry and hard, brownish or black, according as much or little hemoglobin is diffused through the necrotic parts during the mummification (Fig. 16).

Moist gangrene develops when a necrotic part of the body becomes the seat of decomposition. A necrotic tissue which is infiltrated with blood and other fluids offers favorable conditions for infection with saprophytic and other bacteria, in consequence of which decomposition and putrefaction of the tissues take place. These lead to greenish and black discoloration of the parts and to the production of foul odors, various gases, and poisonous substances (among which are ptomaines), until finally softening and total disintegration occur. During moist gangrene the resorption of poisonous products may cause a so-called putrid intoxication (sapremia). Moist gangrene



FIG. 16.—Senile dry gangrene of the lower extremity.

occurs usually in tissues that are naturally exposed to infection with saprophytic micro-organisms, as the lungs, the intestinal canal, the external genitals, the uterus, and the extremities, as well as the cutaneous surface in general. The appearances and consequences of moist gangrene of these

¹ *Jour. Exper. Med.*, ii., 1897.

various organs and tissues are described more fully in the sections on Special Pathologic Anatomy.

The causes that lead to necrosis with consecutive dry or moist gangrene are very numerous.

Diseases of the Blood-vessels.—The most important vascular disease in its relation to necrosis and gangrene is arteriosclerosis. The rigid wall and the narrowings, dilatations, and tortuosities of sclerotic arteries interpose decided obstruction to the blood-current, and favor thrombosis and embolism. It is especially in the extremities that gangrene arises in consequence of arteriosclerosis. The thrombosis may be the primary event, or it may occur secondarily in an already gangrenous part, and causes insurmountable hindrances to the re-establishment of the circulation. Embolism from thrombic deposits upon sclerotic heart-valves or upon rough places in the aorta may be followed by gangrene, because of the insufficiency of the collateral circulation through the diseased vessels and the increased liability to secondary thrombosis on account of the roughness of the wall. Cardiac insufficiency and the resulting passive congestion and edema present conditions that are favorable for the development of moist gangrene.

Nerve-lesions.—Necrosis and gangrene are liable to arise in consequence of central or peripheral nervous diseases involving the trophic innervation, particularly when these are aided by pressure, circulatory disorders, mechanic or thermal injuries.

Symmetric gangrene of the hands, feet, or other parts of the body (Raynaud's disease) has frequently been ascribed to trophic lesions, but undoubtedly some instances depend upon a symmetric arteriosclerosis. There are also peculiar forms of gangrene of the skin, affecting not rarely the external genitals, the causes of which are obscure.

Anesthetic leprosy is usually accompanied by extensive necrosis and ulceration that leads to great mutilation. Here the anesthesia exposes the parts to all forms of external injury, mechanic as well as thermal, and to infection, which undoubtedly plays an important role in causing the necrosis of the enfeebled tissue.

The acute decubitus, or bed-sore, that develops in diseases of the spinal cord is generally attributed to trophic disturbances. On account of paralysis the patient sometimes occupies the same position for a long time, in consequence of which the parts chiefly subjected to pressure are rendered anemic, and this anemia favors the development of necrosis. But the acute decubitus of such diseases as transverse myelitis sometimes develops so rapidly that it can scarcely be the result of pressure, and the disturbance of the trophic and vasomotor innervation seems to be the essential cause.

Extremes of Temperature and Chemical Agents.—Extreme heat and extreme cold directly destroy the vitality of tissues. After exposure to extreme cold—congelation—dry or moist gangrene may follow, depending entirely upon external conditions. Tissues may be destroyed by contact with strong chemical agents, as sulphuric and other acids. Direct mechanic violence, such as crushing injury, also produces necrosis. Thermic, chemical, and mechanic agents may lead to necrosis more indirectly by first so changing the vessels of a part that the circulation is permanently arrested.

Local Pressure.—The formation of a bed-sore in a patient with some severe disease, like typhoid fever, is the result of pressure upon a prominent part, such as the promontory of the sacrum, the pressure causing

anemia and death of the tissue. In many of these cases the weak state of the heart favors the occurrence of necrosis. Secondary infection may ensue and greatly hasten the destruction. The pressure of hard foreign bodies may cause perforation (due to necrosis) of the internal organs, as perforation and gangrene of the vermiform appendix by fecal calculi and perforation of the gall-bladder by biliary calculi.

Ergot-intoxication.—Chronic poisoning with ergot leads to persistent contraction of the arterioles and necrosis from anemia. Kobert¹ produced necrosis in the cock's comb and tongue by feeding with ergot.

In man the necrosis occurs first in the ends of the extremities, and most readily in the case of persons with sclerotic arteries.

Progressive Emphysematous Gangrene.—This is a form of infection with *B. aërogenes capsulatus*, the bacillus of malignant edema, or some other anaërobic bacillus, that results in great serous exudation and immediate death of the tissue, followed by the production of gas. The process spreads very rapidly, and may convert an entire extremity into a swollen, crepitating, greenish mass, infiltrated with serous and bloody fluid. The patient usually dies early from general intoxication.

The necrotic change sometimes produced by the *x*-ray has been called white gangrene ("x-ray burn"). The genesis of white gangrene is not understood. It has been assumed that it results from destruction by the *x*-ray of the nerves of the affected part;² but this theory has not yet been confirmed by histologic examinations in early stages of the necrosis.

From the foregoing it will be seen that necrosis and gangrene may develop under a variety of conditions that frequently operate together. The essential causes are in their nature (a) mechanic, chemical, or bacterial; (b) thermal; (c) anemic; or (d) neuropathic. Regarding the neuropathic causes of necrosis, it must be said that in the majority of instances in which they appear to play a part they are usually associated with circulatory disturbances, mechanic pressure and injury, and bacterial infection, so that it often becomes impossible to say whether the trophic lesions are the essential factor or not.

When gangrene is arrested from any cause, then the necrotic part is loosened from the healthy tissue by a zone of inflammation; after the absorption or removal of the dead tissue regeneration may occur, but the defect usually becomes more or less completely filled with connective tissue.

Necrosis with Softening.—Necrosis with softening, liquefaction, or colliquative necrosis, may occur either primarily or as a change secondary to other forms of necrosis.

Colliquative necrosis occurs primarily in tissues that contain only a little of the fibrin-forming substances, but which are freely bathed in lymph. These conditions obtain particularly in the brain and spinal cord, in which anemic necrosis is regularly associated with softening. The dead tissue changes into a soft mass containing fragments of myelin and broken-down tissue, which gradually become dissolved in the lymph. Admixture with blood and hematogenous pigment may give the softened area a red, brown, or yellow color. A connective-tissue sac may form around the fluid, a cyst resulting; or complete absorption and cicatrization may take place. In the process of resorption of softened and degenerated material large wandering

¹ Ueber die Bestandtheile und Wirkungen des Mutterkorns, 1884.

² Hopkins, Phila. Med. Jour., 1899.

cells filled with detritus and fatty drops and granules, and known as granule-cells, appear. They may accumulate in the sheaths of the vessels.

In the heart-muscle necrosis due to anemia sometimes results in softening. Purulent processes are also accompanied by liquefaction of tissue.

Softening occurs as a secondary process in areas of coagulation necrosis or of mucoid degeneration, in thrombi, and in fibrinous inflammatory exudates, partly as the result of peptonization, partly on account of infiltration with serous fluid. In diseased blood-vessels, together with the formation of new connective tissue in the intima (arteriosclerosis), hyaline degeneration and granular disintegration with liquefaction often take place; cholesterin crystals may appear, as is the case also in other foci of disintegration. The softened mass is often designated atheromatous material. In the stomach and duodenum necrotic tissue is digested by the gastric juice, giving rise to peptic ulcers.

Coagulation Necrosis. Caseation.—Coagulation necrosis is characterized by the formation in the necrotic tissue of fibrin or of substances morphologically similar to fibrin. Theoretically, coagulation of fibrin would result whenever the necrosis furnished the nucleoproteid termed fibrin-ferment, because the surrounding lymph contains fibrinogen, although only in small quantity. That fibrin is actually formed in necrotic foci can be positively demonstrated in many instances by the use of Weigert's specific fibrin stain. Whether all the necroses commonly included under the term coagulation necrosis, in accordance with the teachings of Cohnheim and Weigert, are in reality instances of fibrin formation may perhaps be questioned. Many of the necroses usually described as examples of coagulation necrosis are defined by some as hyaline degeneration (von Recklinghausen), and by others as caseation (Thoma). The truth seems to be that nearly all the conditions referred to are characterized by the formation from the protoplasm of the dead cells, and also perhaps from the tissue-lymph, of solid albuminous bodies that greatly resemble fibrin morphologically, and in many instances at least are forms of fibrin, as shown by their positive reaction with the fibrin stain.

In so far as thrombosis depends upon the liberation of the fibrin-ferment by dying cells, it is in a way correct to refer to the thrombus as an example of coagulation necrosis. Inflammatory exudates of various kinds also undergo coagulation with the formation of fibrinous masses; and in the so-called diphtheric inflammations of mucous membranes there is a more or less extensive necrosis of the mucosa, with the formation of fibrinous clumps and granules, and thick and thin threads, that are in part the result of coagulation of the dead cells, in part due to coagulation of the vascular exudate and of blood-corpuscles.

Many of the focal necroses of toxic and bacterial origin already considered are undoubted instances of coagulation necrosis. Chemical agents, such as the mineral acids, carbolic acid, corrosive sublimate, cause a coagulation necrosis of the tissues with which they come in contact.

Necrosis of striated muscle is followed by transformation of the contractile muscle-plasma into glistening homogeneous masses without transverse striæ. This change was designated by Zenker as waxy degeneration of muscle. Friedreich, Weigert, and others look upon it as due to a coagulation of the muscle-plasma. It is observed especially in febrile diseases, such as typhoid fever; and it is assumed by some that on account of loss in

consistence and firmness, due to the fever and toxic influences, the fibers separate readily upon muscular contraction. The change is found oftenest in the muscles of the abdominal wall and in the adductors of the femur. The same condition is observed in the ends of healthy muscles that have either been torn or cut across. The tears occur preferably parallel to the transverse striæ; the resulting fragments contract slightly, are homogeneous and refractile, and are without transverse striation.

Muscles that have undergone this change in the course of febrile disease present to the naked eye a lusterless, opaque, pale, grayish-red appearance. The regenerative processes that ensue after necrosis in muscles are considered elsewhere.

Occlusion of terminal arteries in the kidneys and the spleen, from embolism or other cause, results in necrosis due to anemia of the parts nourished by the occluded branches, and the so-called *anemic infarct* is formed, which may be changed into a red or hemorrhagic infarct in consequence of a secondary infiltration with blood. In either case coagulation occurs in the protoplasm of the cells and of the intercellular lymph, and, in the case of the red infarct, of the blood-plasma. The cells are changed into homogeneous hyaline masses, lying in a granular or reticulated substance; subsequently the dead tissues disintegrate into a granular amorphous detritus, while the red blood-corpuscles fall into fragments and give rise to pigment particles. During the subsequent changes a hemorrhagic infarct may lose its color.

According to Schmaus and Albrecht, anemic necrosis of the kidney from experimental ligation of the renal artery may be followed by a breaking up of the nucleus of some of the cells into fragments (*karyorhexis*), preceded by a transposition of the chromatin filaments; this they regard as a necrobiotic change in the nucleus. Ordinary karyolysis is observed at the same time. Albrecht believes that in the normal state protoplasm is fluid, and that when coagulation occurs the protoplasm becomes the seat of a precipitation in drop-like form (the so-called *tropfige Entmischung*).

In the course of time infarcts either become absorbed and replaced by a scar, or are encapsulated and infiltrated with lime salts.

Caseation is the term applied to postnecrotic changes that give the dead tissue a similarity to various forms of cheese. The substance is more or less firm, dry or sometimes viscid, and yellowish or grayish-white. Microscopically the mass is granular or contains somewhat homogeneous flakes. The original structure of the tissue is partly or wholly lost, the nuclei are absent or refuse to stain, or are broken up into dust-like particles of chromatin. At times a granular network may be observed, on which account caseation has also been considered a form of coagulation necrosis; but the fibrin is small in amount, and often is entirely absent. The chemical composition of caseous material is not known, and it is very probable that various substances are included under the same name. In many instances the caseous material is more soft, and consists then of a fatty and albuminous granular detritus. It is probable that the variable consistency of caseous material depends upon changes in the amount of fluid present in the area, which again may depend upon local conditions. An interchange of substances by diffusion, or in other ways, probably takes place between the surrounding tissue and the cheesy focus.

Caseation occurs especially in tuberculous areas. It constitutes the

characteristic form of necrosis, or necrobiosis, in the miliary and conglomerate tubercles, and in diffuse tuberculous infiltration. The necrosis that results in caseation is due in part to the poisonous action of the tubercle-bacillus and its products, in part to insufficient blood-supply of the new tissue.

Caseation also occurs in syphilitic areas, in certain rapidly growing tumors, and in some non-tuberculous inflammatory infiltrations in the lungs. The coagulation necrosis of infarcts is sometimes regarded as caseation.

Caseous masses may be completely absorbed; or they may be surrounded by a wall of connective tissue, may undergo softening, inspissation, or calcification.

SIMPLE ATROPHY.

Atrophy is the shrinking of an organ or tissue, due to decrease in the size and number of the cells, without any evident change in structure or in chemical composition. It is a retrogressive process of parts well formed and, in proportion to the age of the organism, well grown.

Atrophy occurs physiologically, as, for instance, in old age, when a varying degree of shrinking takes place in the tissues of the body. Here the shrinking appears to be due to a diminished regeneration of cells that have been worn out, so that what may be called the normal senile atrophy is due not so much to increased waste as to diminished repair.

The thymus undergoes almost complete involution early in life, and the female generative organs become atrophic after the menopause.

The mammalian fetus presents many structures which shrivel and disappear, leaving perhaps but remnants as their functions either become unnecessary or are assumed by other organs. As examples may be mentioned the vitelline duct, many of the vessels concerned in the fetal circulation, the thyroglossal duct, the Wolffian bodies, and various canals connected with the organs of generation.

Simple atrophy, or atrophy in the strict sense of the word, is due to a decrease in the size or number of cells of an organ, or to both these changes, without the intervention of any special changes in the structure or chemical composition of the cells. Degenerative atrophy, on the other hand, is preceded by degenerative changes in the protoplasm and nuclei of the cells, and is a consequence of some of the familiar forms of degeneration about to be described.

The cells microscopically present no demonstrable changes in the earlier stages of simple atrophy, except diminution in size and perhaps a slight change in form, and in some instances an increased pigmentation, as in the heart-muscle and in the liver. In advanced stages the cells may be greatly shrunk and deformed, becoming converted into firm, irregular masses without visible nuclei, disintegration and absorption finally taking place. The increase in pigmentation observed in some tissues may be a real increase in pigment or an apparent or relative one, the pigment becoming more clearly visible as the cells shrink. In the so-called *brown atrophy* of the heart the heart-muscle presents a brownish color, which is readily recognized with the naked eye, and which depends upon an accumulation of a brownish granular



FIG. 17.—Brown atrophy of heart-muscle cells in chronic pulmonary tuberculosis. $\times 260$.

pigment in the vicinity of the poles of the nuclei of the muscle-cells (Fig. 17). Atrophic ganglion-cells are usually highly pigmented; vacuolation and a homogeneous transformation of the cytoplasm also occur, demonstrable by staining with Nissl's method (Fig. 18). When striated muscle undergoes atrophy the fibers become narrow and the striations indistinct; simultaneously there may be increase in the fat, which replaces the disappearing muscle.

Diminution in the size as well as in the weight of atrophic organs depends, as stated, upon the decrease in the size and number of their cells. It is to be noted, however, that in glandular and other organs, as well as in muscles and bones, it is the specific tissue-elements that atrophy, and not the connective-tissue framework. The tubular epithelium of the kidney, the hepatic cells, and the ganglion-cells of the brain and spinal cord may undergo complete atrophy without appreciable decrease in the connective or glia-tissue. In this manner an atrophic organ may become harder and firmer than normal (induration). If the atrophy of an organ occurs in equal degree in

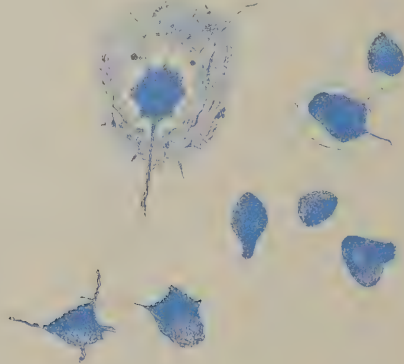


FIG. 18.—Atrophy of the ganglion-cells in the anterior horns of the spinal cord in amyotrophic lateral sclerosis. Fixed in absolute alcohol; stained with methylene-blue (Nissl's method). $\times 300$.

all parts, the surface presents the normal contour; but if it occurs irregularly, the surface becomes uneven and granular.

In the case of the lungs and the bones atrophy may take place without any special changes in external form or volume, the process involving the walls of the pulmonary alveoli, and in the bones the medullary spaces and Haversian canals, the lumen of which becomes enlarged (eccentric atrophy, osteoporosis). The decrease in weight will in such cases give a correct notion of the extent of the atrophy.

Atrophy of the connective tissues, especially of adipose tissue, is of common occurrence.

The **causes** of simple atrophy are manifold, and it is customary to consider the etiologic varieties under the following headings:

The Atrophy of Inactivity or Disuse.—An intimate relation exists between nutrition, function, and growth of tissue. Total or partial functional inactivity leads to diminution in the nutritive supply. The vascular mechanism is so arranged that where the greatest functional activity exists

there the blood-supply is best ; *vice versa*, functionless tissues receive less nourishment. Both inability to perform the functions as well as the removal of the necessity for the functions may lead to atrophy. Inactive parts therefore atrophy.

Loss of the necessity of function appears to be the essential cause of the atrophy or involution of the fetal structures already enumerated, and also of various highly specialized organs in certain animal species. Thus, the eyes of the denizens of the Mammoth Cave of Kentucky are of no service because light never penetrates its vast recesses ; the necessity for the function of vision no longer exists, and hence the eyes of these animals have gradually suffered atrophy, so that at the present time the descendants of animals once possessing perfect eyes have only blind remnants. In several forms of deep-sea fishes, especially those which have descended to such great depths that few if any rays of light reach them, the eyes are rudimentary, and in some cases are covered with skin (Bland Sutton).¹

Atrophy from inability to carry on function is well illustrated in the great wasting which occurs in all the structures of an extremity rendered functionally inactive or useless by a tumor, a serious deformity, or on account of paralysis.

Pressure-atrophy.—Atrophy takes place when a tissue is exposed to prolonged increase in the normal pressure. This form of atrophy is frequently observed in the course of various pathologic processes. It undoubtedly depends in part upon circulatory disturbances, in part upon direct injury to the cells. Pressure-atrophy is illustrated by the shrinking of the liver-cells adjacent to a distended central vein the seat of passive congestion ; by the gradual disappearance of parenchymatous cells when compressed by contracting cicatricial tissue, as in chronic interstitial myocarditis and cirrhosis of the liver ; by the so-called "corset liver," the characteristic deformity of which is due to atrophy of the liver along the line of pressure by the costal arch ; by the hollowing out and disintegration of the vertebræ (Fig. 19) and parts of the bony thorax under the continuous pressure of aneurysms of the aorta ; and by the thinning of the skull in various forms of increased intracranial pressure.

Senile and Marantic Atrophy.—Atrophy occurs to a marked degree in the condition described as premature senility, and in certain diseases and conditions accompanied by great wasting and exhaustion (marasmus). The atrophy of premature senility may be considered theoretically as due to the scanty power of regeneration and repair of congenitally imperfect and enfeebled cells. Practically, however, the diminution of arterial blood-supply due to disease of the arteries, and disturbances



FIG. 19.—Disintegration of the bodies of the vertebræ due to the pressure of a thoracic aneurysm.

¹ General Pathology.

of nutrition on account of diseases of the digestive tract or of the nervous system, often appear to play an essential role.

The general atrophy that occurs in starvation must be ascribed to absence of nourishment; the atrophy of chronic wasting diseases, such as tuberculosis, carcinoma, leukemia, and also of certain acute infections, may be attributed in part to deficient nourishment, and in part to general poisoning with toxic substances produced by the morbid processes which directly lower the vitality of the cells. The atrophy in these conditions is frequently accompanied by degenerations of various kinds. Imperfect regeneration also plays a part in the resulting atrophy. Local interference with the blood-supply, as occurs in consequence of diseases of the arterial walls, causes local atrophy when the anemia develops gradually; sudden, absolute anemia is followed by necrosis.

Neurotic Atrophy.—The state of the central nervous system is of great importance as regards the nutrition of the body. The classic examples of neurotic or neuropathic atrophy are seen in the rapid wasting of the muscles (Fig. 20) and of the nerves after destruction or disease of the anterior horns

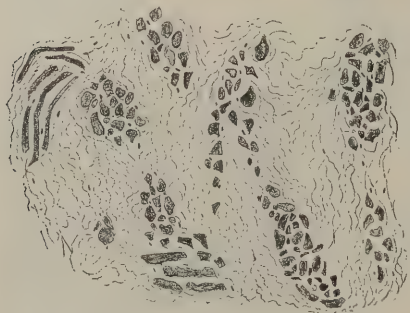


FIG. 20.—Atrophy of skeletal muscle following degeneration of the ganglion-cells of the anterior horns of the spinal cord. $\times 175$.

of gray matter in the spinal cord and of the bulbar nuclei. The ganglion-cells in the anterior horns are the trophic centers of the motor neurones of the second order, and exert also marked trophic influences upon the corresponding muscles. Undoubtedly many factors operate in producing the muscular atrophy of central origin: the paralysis that follows removal of the nerve-supply induces inactivity; vasomotor disturbances are certainly present, which may cause further nutritive disorders; and then the

probable direct trophic influence of the ganglion-cells is also removed.

In disease of the nerves of the face *facial hemiatrophy* sometimes develops; and fetal or infantile diseases of a cerebral hemisphere may be followed by atrophy of the opposite half of the body. In rare cases the hemiplegia of adults, though dependent upon a cerebral lesion, is followed by an atrophy that is only in part explicable by disuse; in part it seems to be trophic.

The term atrophy is applicable to the retrogressive processes above outlined, as it occurs in tissues or organs well formed and developed, in contradistinction to hypoplasia and aplasia, which are terms used to designate imperfect developmental conditions. *Hypoplasia* is the incomplete development of a part of the body. Growth may be arrested during fetal life or during the postnatal period of development. Hypoplasia may depend upon causes originally present in the germ-cells, or upon external influences that arrest or limit the further growth of the "anlage." When the arrest occurs late in fetal, or in postnatal, life the nature of the condition seems to correspond to certain forms of atrophy. Thus, diseases of the thyroid gland, or disuse in consequence of deformity or inflammation, may limit or disturb the normal growth of growing bones, and absence of the ovaries may arrest the

growth of the uterus. On the other hand, many such conditions as are observed in some dwarfs, in the rudimentary development of extremities, and in the almost complete absence or limited development of many organs, such as the brain, the intestines, the kidneys, the lungs, the uterus, and the liver, must be referred to causes inherent in the germ-cells, or to diseases and accidents in the earliest periods of fetal life.

If an organ or part of the body fails entirely to develop, the condition is one of *aplasia*, or *agenesia*; it may depend either upon a congenital absence of the "anlage" in question or upon a direct destruction or complete atrophy of the part after its development had begun. The further consideration of hypoplasia and aplasia belongs to teratology.

DEGENERATIONS AND INFILTRATIONS.

Amyloid Degeneration.—Amyloid, waxy, or lardaceous degeneration is a peculiar retrogressive process due to the formation or deposition in various organs of a serum-albumin of slight solubility and of a homogeneous appearance, which gives a mahogany-brown color reaction with iodine, and a rose-red with methyl-violet or gentian-violet.

Amyloid degeneration develops, as a rule, in several organs at the same time, but without any regular order; most frequently it occurs in the spleen, the liver, the kidneys, the stomach, the intestines, the pancreas, the adrenals, the thyroid gland, and the lymphatic glands; but it may also occur in the heart, the aorta, the muscles, adipose tissue, the uterus, and the ovaries.

Organs the seat of advanced amyloid degeneration are usually much enlarged. In the case of the liver the margins are thick and rounded, the consistency greatly increased, so that the organ is firm and rather inelastic; the cut surface presents large, irregular areas of a dry, somewhat glistening, homogeneous appearance, and thin sections of it are translucent and not unlike the fat of bacon. The translucent areas stain brown with watery solutions of iodine. When the process is less pronounced, in its early stages, or when it is accompanied by fatty or other changes, or when it occurs in localities such as the heart, the aorta, or in adipose tissue, it may be necessary to resort to microchemical examination in order to demonstrate the presence of amyloid material.

The characteristic iodine reaction of amyloid material is obtained in the following manner: First the blood is washed from the surface with water; then the reaction of the tissue is rendered acid by pouring over it a little acetic acid, although this is not absolutely necessary; this is followed by a short bath in a solution of iodine in iodide of potassium (iodine, 1 part; potassium iodide, 10 parts; distilled water, 100 parts), which is washed away with water. The amyloid material will be found stained a deep reddish-brown or mahogany-brown, while the surrounding tissue is of a straw-yellow color. Microscopic sections of fresh tissue, made with the double knife or freezing microtome, may be stained in precisely the same manner. It is well, however, to use a more dilute iodine solution. Under the microscope the amyloid material is of a brighter reddish-brown color. The iodine reaction is also obtainable with hardened tissues.

The acetic acid is added in order to insure an acid reaction of the tissue; when the tissue has become alkaline in reaction from decomposition, then the

brown color of the amyloid material may fail to develop, on account of the formation of the alkaline iodids. If the tissue, after having been stained brown with iodine, is treated with dilute sulphuric acid (5 per cent.) or a solution of chlorid of zinc, the amyloid areas become very dark brown, grayish-brown, violet, greenish-blue, or blue. This reaction is inconstant, and the colors are generally a little mixed.

Oddi and also Krawkow have recently shown that amyloid substance is a compound of chondroidin-sulphuric acid and albumin. Krawkow found this compound a normal constituent of cartilage and all structures rich in elastic tissue, particularly in the blood-vessels. In its pure state amyloid is entirely free from phosphorus and does not give the iodine, but gives the methyl-violet, reaction. The iodine reaction as ordinarily obtained seems to depend upon physical conditions, the amyloid substance assuming the brown color with iodine when in a compact state.

For the purpose of a closer microscopic study of tissue the seat of amyloid degeneration, the staining with methyl-violet or gentian-violet solution gives the best results. The microscopic sections of fresh tissues or of tissues hard-



FIG. 21.—Amyloid degeneration of the kidney in chronic pulmonary tuberculosis: *a*, degeneration of the capillary network of a glomerulus and of the wall of the afferent vessel; *b*, degeneration of the media of a small artery. Alcohol hardened, stained with methyl-violet, decolorized with acetic acid; amyloid material pinkish red, normal tissue bluish. $\times 75$.

ened in alcohol or formalin are brought for a few minutes into a watery solution of methyl-violet; they are then washed in acetic-acid water, mounted, and examined in glycerin. The amyloid material will be stained a bright or ruby-red, while the surrounding tissues are blue or bluish-violet (Fig. 21). By careful decolorization in the acetic-acid water the nuclei of the tissue will appear deep violet, while the amyloid substance is bright red, so that the relation of the amyloid material to the cells of the tissue in which it is found can be made out very clearly.

By studying such preparations it is found that amyloid material is formed or deposited primarily in the ground-substance of the blood-vessels and the connective tissue, especially in the middle coat of the smaller arteries.

In the kidneys the process commences in the intertubular arteries and in the capillary tufts of the glomeruli. Homogeneous masses of varying size and shape seem to crowd the muscular fibers of the media apart, while the endothelial lining remains intact. The muscle-cells may show irregularities in form, due to shrinking or atrophy from pressure, and in many cases the

entire media may appear to have been replaced by amyloid material. The capillary loops of the glomeruli are greatly swollen and homogeneous, and the amyloid material may appear between the tubules of the kidney outside the vessels as well as in the tunica propria of the tubules.

In the liver the amyloid material appears first between the capillary endothelium and the rows of liver-cells; here it forms thick, homogeneous layers, between which are partly normal, partly atrophic, or fatty hepatic cells. Amyloid material does not appear to develop in the interior of the liver-cells. In the gastro-intestinal mucous membrane the amyloid material appears first in the walls of the vessels; in the spleen the walls of the smaller arteries and veins are usually involved, but the degeneration quite often confines itself to the Malpighian bodies, which may become greatly enlarged and not unlike grains of boiled sago (*sago-spleen*); the trabeculae and fibers of the reticulum also become thickened. In fat tissue the amyloid material may appear in the walls of the vessels as well as in the fibrous tissue and in the membrane of the fat-cells; and in striated muscle it develops in the internal perimysium and the sarcolemma. The occurrence of amyloid degeneration of the muscle-cells proper has not been proved to general satisfaction.

On account of giving a brown color reaction with iodine and a blue color with sulphuric acid and iodine, Virchow¹ saw a certain resemblance between amyloid material and starch; and hence the name amyloid, which he originated. While starch (*amylum*) is a carbohydrate, Kekule and Friedreich, and others, soon demonstrated that amyloid material is an albuminous body, characterized by insolubility in water and by great resistance not only to acids and alkalies, but also to the action of gastric juice and to decomposition.

The causes of amyloid degeneration are not clearly understood. Observation has established the fact that in the majority if not in all of the instances it occurs as a secondary process in certain general, chiefly infectious, diseases accompanied by grave disturbances of nutrition. It is especially in connection with chronic tuberculosis (lungs, bones, and joints), chronic suppuration (osteomyelitis, actinomycosis), severe forms of syphilis, and chronic dysentery, that extensive amyloid degeneration takes place. Carcinoma, leukemia, and severe malarial infection occasionally lead to amyloid degeneration; and Ziegler states that at times it develops without any preceding disease. Bland Sutton remarks that in horses amyloid degeneration may occur independently of previous disease. Czerny claims to have produced it in dogs by long-continued experimental suppuration due to injection of turpentine, but Krakow and Lubarsch were not able to confirm this statement. Krakow² describes a series of experiments in which he claims to have succeeded in producing amyloid degeneration in rabbits and in chickens by the repeated injection, in increasing quantities, of bouillon cultures of *Staphylococcus pyogenes aureus*. He also produced amyloid change by using the toxin of *Bacillus pyocyaneus*. The degeneration appeared in from one and one-half to two months after beginning the injections. Cohnheim observed that in man the degeneration could develop in from two to three months. Maximow and Davidsohn have also produced amyloid material by experiments similar to those of Krakow.

While it is evident that amyloid degeneration stands in close relation to

¹ Virchow's *Archiv*, v., vi., viii., xi.

² *Arch. de méd. exp. et d'anat. pathol.*, x., 1898.

the general nutritive disorder and the chronic intoxication (cachexia) present in the diseases mentioned, and also in the animals experimented upon, yet the exact histogenesis of the amyloid material remains unexplained. Several hypotheses have been advanced. Thus, it has been thought that the parenchyma-cells are directly changed into amyloid substance; but this theory does not accord with the microscopic appearances, which clearly show that the material first appears in the ground-substance of the connective tissue and the vessels. Von Recklinghausen¹ advances the hypothesis that the cells of the organs affected eliminate a homogeneous material which stiffens in the tissue-spaces into the characteristic masses of amyloid material. The insolubility of amyloid material would seem to exclude the idea that it could circulate dissolved in blood and be deposited in the tissues. The constancy with which the material appears in the walls of the vessels points, however, to some relation between its formation and the blood; and at the present time the general opinion seems to be that in the diseases in connection with which the degeneration appears there is present in the blood a substance which is either precipitated or deposited in the tissues as amyloid material or unites with the tissue-juices to form this peculiar substance. If it is possible, as seems to have been shown, that amyloid degeneration may be produced experimentally, the question concerning the histogenesis of the material will undoubtedly receive further elucidation. Czerny has advanced the opinion that in the early stages amyloid material is formed in the local foci of suppuration, and is carried to the internal organs by the leukocytes. He bases this opinion upon finding cells giving the amyloid reaction in the pus and in the blood of animals showing later amyloid degeneration of the spleen.

Amyloid degeneration is always fraught with serious consequences. As far as is known at the present time, amyloid material once formed is probably not reabsorbed. Krakow showed that in the rabbit experimentally produced amyloid degeneration of the spleen might disappear by absorption of the material, but it is not known that this can occur in man. A probable exception to this statement is the fact observed by Raehlmann and others, that so-called amyloid tumors of the conjunctiva may undergo complete absorption after partial removal. When amyloid material is introduced into the peritoneal cavity of rabbits it is gradually removed by giant cells, which shows that the material is susceptible of absorption. Giant cells enclosing amyloid material have also been found in local amyloid deposits (see below). While the diseases that lead to amyloid degeneration are of the most serious nature, it is evident that the permanent tissue-changes induced by this process must tend to aggravate the grave general condition that already exists. Thus, the changes in the vessel-walls lead to narrowing, and even occlusion, of the lumen, with permanent disturbance of the circulation; and the pressure of amyloid masses upon the adjacent cells causes atrophy. Fatty degeneration and atrophy of the special tissue-cells are consequently always observed in organs undergoing the amyloid change, partly as the direct result of the local action of the amyloid material, partly as the result of the general cause that gave rise to the amyloid degeneration.

Local Amyloid Formation and Corpora Amylacea.—In addition to the general amyloid degeneration, which usually involves several organs at the

¹ *Allg. Path. des Kreislaufes und der Ernährung*, 1888.

same time, and which develops under special conditions, there occurs also, undoubtedly from local causes, a purely local amyloid formation, either in the form of amyloid infiltration of tissue, to which belong the so-called amyloid tumors, or as free amyloid concretions.

Local infiltration of amyloid material has been observed in cellular granulation-tissue, as in the conjunctiva and in ulcers of the leg, in scars and chronic connective-tissue proliferations, as, for instance, in syphilitic cicatrices of the liver and of the larynx, as well as in syphilitic lymphadenitis, and also in various tumors—*e. g.*, of the larynx and of the stomach. Usually the amyloid substance occurs in small masses, but occasionally also in larger foci; the material appears in the ground-substance of the tissue and in the vessel-walls; although some authors state that the cells themselves may become hyaline and give the amyloid reaction (Raehlmann). The amyloid material has frequently been observed in these situations in connection with hyaline degeneration.

Tumor-like amyloid masses without any definite connection with inflammatory processes are also occasionally met with, especially in the conjunctiva, the root of the tongue, the larynx, and the trachea. These masses may reach considerable size and become very hard; they are commonly called amyloid tumors.

Free amyloid concretions, or corpora amylacea, are found almost constantly in the tissues of the central nervous system. They occur especially in the ependyma of the ventricles, but also elsewhere in the brain and spinal cord, more particularly in areas in which the nerve-fibers have undergone degeneration.

Corpora amylacea occur also quite regularly in the follicles of the prostate (Fig. 22) after puberty; furthermore, in the lungs, in fibrinous exudates, hemorrhagic extravasations, and chronic fibroid processes, or free in the alveoli in emphysematous parts. They have also been found in carcinomas.

These bodies, which usually give the amyloid reaction with iodine, present in the main a concentric arrangement; in the center may be irregular fragments or masses, or hematoidin crystals in case they have formed in hemorrhagic foci, as in a pulmonary infarct; those found in the central nervous system are usually small compared with those from the prostate. It is generally believed that they are formed by the coalescence of the remnants of desquamated and degenerated cells.¹ In the nervous system some believe they arise from the nuclei of the glia-cells, while others claim they are developed from the fragments of degenerated axis-cylinders. In many

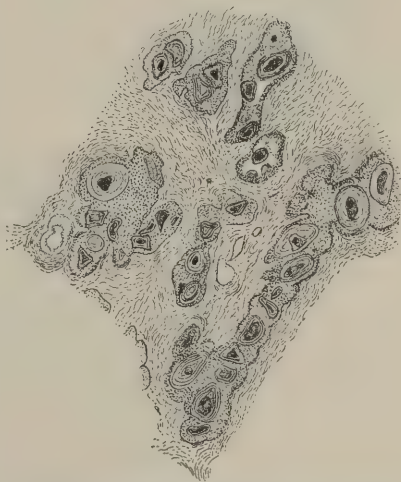


FIG. 22.—Amyloid concretions (corpora amylacea) in the gland-tubules of the prostate of a man thirty-two years old. $\times 150$.

¹ Seigert, *Virchow's Archiv*, cxxix, 1892.

respects some of the amyloid bodies resemble the globular hyaline formations to be described.

Hyaline Degeneration.—Hyaline degeneration takes place especially in connective tissue, and renders it homogeneous and structureless. The hyaline substance into which the connective tissue is converted or by which it is replaced has not yet been shown to have a distinct chemical entity; it resembles amyloid material, but is distinguished from it by the absence of the iodine reaction. Hyaline material has no constant staining reaction, although with Van Gieson's stain it assumes a bright-red tinge. Like amyloid degeneration, hyaline also attacks by preference the walls of the blood-vessels; but hyaline degeneration does not show any such marked etiologic relation to chronic suppuration and infection as amyloid, and its distribution in the body is more erratic.

In the walls of the smaller blood-vessels the hyaline material appears first outside the endothelial lining, in the form of homogeneous masses. Gradually the wall becomes thicker and the lumen smaller; and finally the latter



FIG. 23.—Hyaline degeneration of the glomeruli and colloid material in the tubules in the vicinity of an anemic infarct in the kidney: *a*, colloid material; *b*, hyaline glomeruli with much round-cell infiltration about them. $\times 150$.

may disappear entirely. Hyaline degeneration of the smaller vessels is observed in the capillary tufts of the glomeruli of the kidney (Fig. 23), in the brain, in the lymph-glands, and also in the meninges in tuberculous meningitis (Fig. 24). In the last it might be confounded with caseation were it not for the fact that it often occurs in the walls of vessels surrounded by recent tuberculous proliferation in which no degeneration has occurred (Guarnieri).

Hyaline degeneration also occurs in the thickened intima of sclerotic arteries, and in heart-valves the seat of chronic fibrous endocarditis. In these localities the hyaline material frequently becomes softened and infiltrated with calcareous particles. It is also found in the connective tissue of the myocardium, the intestines, in old scars, in the stroma of many tumors, and in the thyroid gland (Fig. 25), especially when goiter is present. The connective tissue becomes homogeneous and structureless, the nuclei disappearing almost entirely, while the specific tissue-elements gradually atrophy.

The exact cause of hyaline degeneration is not understood. It occasionally occurs in conjunction with amyloid degeneration; but any close relation

between the two changes has not been demonstrated. Neither has it been determined whether the process is essentially one of degeneration or infiltration.

The so-called hyaline bodies (Russell's fuchsin bodies) are peculiar globular, homogeneous, extracellular and intracellular formations of vary-

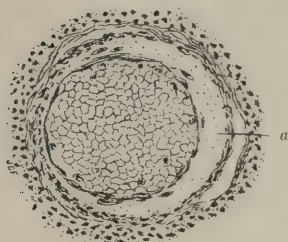


FIG. 24.—Hyaline degeneration of the media of a small artery in the pia in tuberculous meningitis: *a*, hyaline media, much infiltration with cells in the adventitia. $\times 200$.

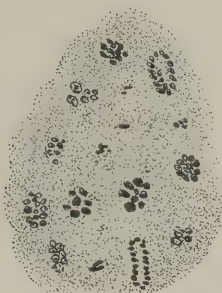


FIG. 25.—Hyaline degeneration of the stroma in the thyroid gland in fibrous goiter. $\times 75$.

ing size; frequently they are aggregated in mulberry-shaped conglomerations. They stain red with the acid-fuchsin, and deep blue with the Gram-Weigert stain (Fig. 26). These bodies occur in many normal tissues and in a great variety of pathologic processes, a favorite place for their study being glandular proliferations of the mucous membrane of the stomach (Hansemann, Thorel); their frequent presence in malignant tumors

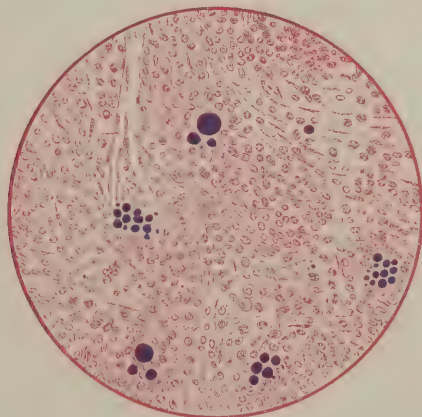


FIG. 26.—Hyaline bodies; chronic appendicitis; carmin and Weigert's stain. $\times 250$.

has led to their being regarded as "cancer parasites" of blastomycetic nature. It is believed that the granules in the oxyphile and basophile cells that are found where organic material is breaking down from any cause may give rise to hyaline bodies, the process partaking of the nature of coagulation. The exact chemical composition of hyaline bodies is not known.

According to its origin, hyaline material as it appears in these bodies may be spoken of as mesoblastic, epithelial (keratohyalin), and blood hyalin (Lubarsch).¹

Degenerative changes in glia-cells may produce glistening masses that stain black with the Weigert-Pal method, red with Van Gieson's method, and bright blue with Weigert's fibrin stain after fixation in Zenker's fluid. First described by Rosenthal, this degeneration has been studied by Barker,² who called it *degeneratio micans*, and showed that the peculiar masses form within glia-cells. So far, *degeneratio micans* has been observed only in gliomas of the spinal cord.

Colloid Degeneration.—Colloid material in its appearance resembles stiffened glue. The substance is usually semisolid, translucent, homogeneous, structureless, and yellowish or brownish in color. The term colloid material does not imply any definite chemical entity. The material differs from mucus in its reactions; unlike the latter, it does not swell in water, is not coagulated by acetic acid, nor is it made turbid by alcohol or chromic acid.

Colloid material occurs physiologically in the follicles of the thyroid gland and the hypophysis; here it is produced by the cells lining the follicles, and, according to a number of investigators, is taken up, as far as the thyroid is concerned, by the lymphatics. Concerning the physiologic importance of this secretion, which contains iodine in the form of thyroiodin, more will be said in the section dealing with the thyroid gland.

An excessive production of colloid material is often observed in the thyroid gland; the follicles then are greatly enlarged and filled with homogeneous masses, so that the gland is much increased in size. The formation of these masses takes place by the coalescence of numerous small drops which arise in the interior of the cells of the follicles, whence they are extruded; at times the entire cell is converted into colloid substance. Similar colloid masses sometimes form by degeneration of the hypophysis. Colloid material, or material of exactly similar microscopic appearance, but in all probability not containing iodine, is often found in the uriniferous tubules and retention cysts of diseased kidneys, and is apparently the result of a degeneration of the epithelial cells. The so-called colloid degeneration in certain forms of carcinoma is probably mucoid in its nature; but in the absence of microchemical reactions and of a definite knowledge of the chemical composition of these jelly-like substances, a correct classification of the obscure changes that lead to their development is not possible.

With Van Gieson's stain colloid material usually strikes an orange-red color.

Mucoid Degeneration.—Mucoid degeneration is the transformation of living tissue into mucus, a transparent, homogeneous, viscid substance. Mucus is a generic term embracing various chemical compounds, known as mucins and pseudomucins. The mucins are nucleo-albumins, and contain nitrogen and sulphur; they swell in water, are precipitated by alcohol and by acetic acid, and are not dissolved in an excess of the acid. They are non-diffusible substances. The pseudomucins are soluble in water and are not precipitated by acetic acid (Hammersten).

Mucus occurs physiologically upon mucous membranes and in mucous

¹ For references, consult *Progressive Medicine*, March, 1899, 241.

² *Am. Jour. Med. Sci.*, cxviii., 1899.

glands, in the contents of joints, tendon-sheaths, and bursas, and in the umbilical cord, where it forms a homogeneous, jelly-like ground-substance. In the mucous membranes the mucus appears especially in the so-called goblet-cells, the protoplasm of which changes into a roundish mass of mucus that appears to fill the cell like a goblet. The mucus formed in the protoplasm of these cells is evacuated and the cells retain their vitality.

The so-called catarrhal inflammations of mucous membranes are characterized by an excessive secretion of mucus by the surface epithelium and the mucous glands. The number of goblet-cells in the membrane appears to be greatly increased (Fig. 27). Furthermore, many of the cells may undergo a total mucoid degeneration of the nucleus as well as of the body, leading to the destruction of the cell. The exudate may contain masses of mucus, in which fragments of such cells are recognizable. The ordinary pus-corpuscles in the exudate may also change into mucus.

Mucoid degeneration also takes place in the epithelial cells of tumors, more especially in carcinomas that originate in the mucous membrane of the gastrointestinal tract, and in the ovarian cystadenomas. Here it occurs chiefly as a mucoid disintegration of the cells, leading to the formation of large homogeneous, structureless masses. In the ovarian cystomas the degeneration results largely in the formation of pseudomucin (Pfannenstiel).

Mucoid degeneration also occurs in the connective tissues; here it is principally the ground-substance that is changed into mucus, although the cells are liable to become involved. Thus, the connective-tissue framework of carcinoma may be transformed into mucoid material. Mucoid degeneration occurs in cartilage and in bone as a senile, retrogressive change, and is also frequently observed to take place in the various mesoblastic tumors, including sarcoma. In such cases the intercellular substance becomes soft and viscid; small clumps of mucus form in the cells, which finally disintegrate and disappear more or less completely.

In the disease known as myxedema, which depends upon disturbance of the functions of the thyroid gland, the subcutaneous tissue is changed into mucoid (myxomatous) material. The exact pathogenesis of this peculiar change is not known.

Mucoid degeneration is, on the whole, a rather mysterious process, the significance of which is not clear nor is its exact etiology understood. It depends upon a chemical process, in which the tissue is changed into mucus. The excessive secretion of mucus in catarrhal inflammations may be looked upon as a favorable feature, in that it protects the membrane, and limits the growth of the invading micro-organisms. Mucus is not bactericidal, but affords a poor soil for the growth of micro-organisms.

According to Levene,¹ the acid radicals in amyloid, mucoid, and colloid materials are similar (chondroidin-sulphuric acid).

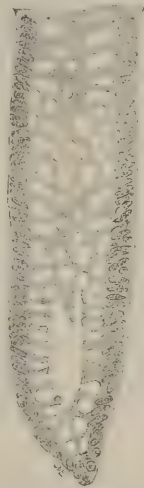


FIG. 27.—Mucoid degeneration of the cells of a tubule in the mucous membrane of an inflamed vermiform appendix. $\times 450$.

¹ *Med. Rec.*, 1900.

Cloudy Swelling and Fatty Degeneration.—If one carefully examines the kidney, the heart, or the liver, of persons who have died of typhoid fever, septicemia, or other acute infectious or toxic disease, it will be found that the organ is relatively a little larger than normal, that the consistence is not so firm, but is rather flaccid, and that on the cut surface the tissue presents a grayish-yellow, turbid or opaque, sometimes shining appearance, as though it had been boiled, while the finer markings characteristic of the organ are indistinct; the organ usually contains but little blood.

In a fresh microscopic preparation, made by carefully scraping the cut surface with a knife or by teasing and mounting some of the particles in physiologic salt solution, the cells will appear larger than normal; they are swollen, the protoplasm is clouded and covered with innumerable opaque granules, among which may be refractile glittering points or droplets with darker outlines, so that it is difficult to see the nucleus (Fig. 28), while the finer markings peculiar to certain cells, as those of the kidney, or the



FIG. 28.—Cloudy swelling of the epithelium of the convoluted tubules of the kidney in puerperal septicemia (general streptococcal infection): *a*, cell after application of a weak solution of acetic acid; the granules have become dissolved, but the fat-droplets remain. Fresh teased specimen. $\times 1000$.

striations of the heart-muscle, are no longer clearly discernible. If the physiologic salt solution be replaced by a 1 per cent. solution of acetic acid, which is allowed to run in under the cover-glass, the fine, dust-like granules are dissolved, the protoplasm becomes clear and the nucleus distinct, while the glistening droplets are undissolved, and are recognizable as particles of fat (Fig. 28, *a*). If alcohol or ether be used with another preparation, the granules are unaffected; but the fat dissolves, leaving holes in the protoplasm of the cell. In such preparations cells will be found from which the nucleus has almost entirely disappeared, so that it is not to be seen even after the application of the acetic-acid solution; and some cells will appear to be disintegrating into granular and fatty detritus.

In a given case the relative quantity of fat-droplets and dust-like granules varies in different cells. According as the one or the other of

these changes predominates, the condition is spoken of as cloudy swelling (parenchymatous degeneration) when the granules are most numerous, or as fatty degeneration when the droplets predominate.

Cloudy swelling, parenchymatous, or albuminous degeneration, is, then, a retrogressive process in which the tissue elements disintegrate into albuminoid granules. The free granules described are regarded as albuminoid, because they are soluble in acetic acid, but insoluble in alcohol and ether. The cells affected become clouded, diffusely granular, the normal structure and form are altered, and there is a slight but evident increase in the size of the cells, probably due to the absorption of fluid. The normal granulation disappears. Very often particles of fat are also formed in the protoplasm.

A certain degree of cloudy swelling is compatible with continuance of function and may subside, the cell resuming its normal structure; often, however, the nucleus swells and disappears, while the cell crumbles into a granular or granular and fatty detritus (Fig. 29).

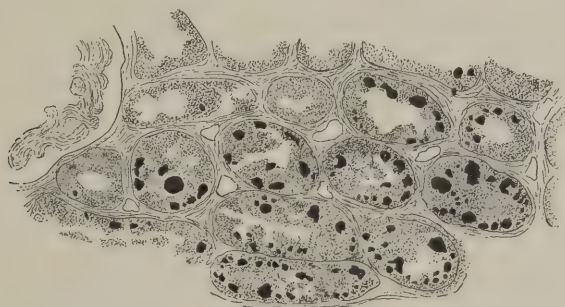


FIG. 29.—Granular and fatty disintegration of the cells of the convoluted tubules in puerperal eclampsia. Fixed in Flemming's solution; stained with safranin. $\times 300$.

Cloudy swelling develops especially in parenchymatous cells, as those of the liver, the kidney, the heart, and other organs; but it may also affect the cells of the stroma of organs, as well as migratory cells.

Fatty degeneration occurs, generally speaking, under the same conditions as cloudy swelling, with which it is closely related and often associated. It appears in the form of minute droplets and particles of fat in the interior of the cell, the protoplasm of which is clouded and granular. Later in the process larger globules of fat may form. The fat appears under the microscope as colorless, glistening, refractile particles and droplets with dark outlines; it is insoluble in acetic acid, but soluble in ether and alcohol, and stains black with osmic acid (Figs. 28 and 29). When the process has developed to a marked degree it gives the tissues an opaque, grayish, yellowish-white or yellow appearance that is either uniformly or irregularly distributed. When advanced it leads to disintegration of the cells into fatty and albuminous molecules—fatty necrobiosis—and may result, after removal of the detritus, in a marked diminution in size of the affected organ. But within limits this retrogressive process is also compatible with a certain degree of function and with complete “*restitutio ad integrum*,” in which case the fat is either oxidized or taken away and redeposited in the usual fat depots.

So-called fatty degeneration—degenerative lipogenesis—is generally regarded as a disintegration of the protoplasm of cells into fat. The fat is thought to be produced at the direct expense of the cell protoplasm, and not, as in fatty infiltration, from the constituents of the food. Bauer's experiments illustrate well the metamorphosis of protoplasm into fat. Bauer produced the highest degree of fatty accumulation in the protoplasm of the cells by phosphorus-poisoning in dogs that had lost all their fats through a long period of starvation. Taylor¹ has recently pointed out that, from the chemical point of view, it has not yet been satisfactorily demonstrated that fat is ever formed from cellular proteid. The fact that in fatty degeneration the cells suffer marked protoplasmic and nuclear lesions is regarded by Lindemann² and others as good evidence of the origin of fat from the cell protoplasm. Granted that fat forms in degenerated cells, it can still be urged that it is produced from carbonaceous compounds in the cells. This holds true also in regard to the development of fat in epithelial cells after death (Wentscher, Lindemann, and others). The question is an open one. It is important to bear in mind that fatty degeneration is associated with histologic changes in the cells; whereas fatty infiltration (page 100) corresponds with physiologic lipogenesis, and the cells suffer no other changes than those of pressure. For the present the term fatty degeneration should be used rather in the sense of cell degeneration associated with the formation of fat than of cell degeneration into fat.

Degeneration with the formation of fat occurs especially in the cells of the parenchymatous organs; but it may like cloudy swelling attack almost any kind of cell, inclusive of the ganglion-cells of the nervous system.

The concurrence of cloudy swelling and degenerative lipogenesis indicates that these changes are due to essentially the same causes. The formation of fat represents a more advanced stage of the degeneration than cloudy swelling, and is the result of a longer continuance or of a greater intensity of action of the special cause at work. The changes depend upon disturbances of cellular metabolism; they occur particularly in connection with local and general anemia. When a tissue, as, for instance, the heart muscle, receives a diminished quantity of blood on account of narrowing of the lumen of the arteries, due to thrombosis, embolism, or diseases accompanied by thickening of the intima, albuminous and fatty changes usually result. And in the case of the general anemias—secondary anemia, pernicious anemia, or leukemia—it is usual to find an extensively distributed degeneration with fat-production in the liver, the kidneys, the heart, and the skeletal muscles. In these and similar local and general conditions a lasting diminution in the supply of oxygen exists—there is not enough oxygen and other nutritive material to maintain the function of the cells. In actual starvation there is first absorption of all the fat in the body, accompanied by a marked diminution in the volume of many organs, and in the later stages albuminous and fatty disintegration of the kidneys, the liver, and other tissues.

The albuminous and fatty changes that occur in febrile diseases are regarded by some as due, in a certain measure, to the functional increase necessary to the production of the greater heat, especially as regards the organs that are the most important sources of heat, namely, the heart and liver. In febrile diseases, however, the direct action of the poisonous

¹ *Am. Jour. Med. Sci.*, cxviii., 1899; *Jour. Exper. Med.*, iv., 1899.

² *Ziegler's Beiträge*, xxv., 1899.

products produced by the bacteria and by the diseased body enter also into action.

Albuminous and fatty degenerations occur in practically all general infectious diseases, and in a large number of intoxications with various substances, such as phosphorus, arsenic, iodoform, chloroform, sulphuric and nitric acids, alcohol, carbonic oxid, and many bacterial products. In some of these instances of fatty and albuminous changes the precise cause of the degeneration must be sought in abnormal metabolism, due to the direct action of poisons which disturb the normal processes of oxidation. The changes at times occur to a more marked degree in certain localities than in others; this irregular distribution is attributable to the accumulation of the poisons in the organs specially affected. The production of the degenerations in some of these cases, as in the infectious diseases, may be aided to a great extent by diminution in the amount of oxygen taken in and by the action of the fever, as was mentioned above. Many of the substances named, as well as bacterial poisons and the toxic products produced in diseased organs, are eliminated by the kidneys and the liver, and here may be found an explanation of the extensive changes observed in the cells of these organs.

Virchow¹ regarded cloudy swelling as an anomaly of nutrition of a progressive character, believing that under the influence of the so-called inflammatory stimulus the cells absorbed so much nourishment that their structure became more or less disordered. It is hardly necessary to point out that microscopic appearances, the association with fatty degeneration, the frequent termination of the process in disintegration, and the absence of karyokinesis, all demonstrate that cloudy swelling is a change of retrogressive tendency.

Glycogenic Infiltration.—Glycogen is a carbohydrate formed in the body from the food and readily convertible into sugar. It is found in the tissues either in solution or in the form of hyaline, oval flakes, granules, or drop-like masses, lying in the cells or in the intercellular substance. It is easily soluble in water, especially when found in the liver, kidneys, and muscles; while that found in cartilage cells and surface epithelium is dissolved with some difficulty. It is readily demonstrated in the tissues because of its microchemical reaction with iodine, which stains glycogen a brownish-red. It is distinguished from amyloid material by not giving the reaction with iodine and sulphuric acid, and by being soluble in water. On account of its solubility in water the iodine is best applied in the form of an iodinated solution of gum arabic (Ehrlich)² or of a mixture of iodine and glycerin (Barfurth). According to Langhans,³ pieces may be fixed in absolute alcohol, cut into sections, and stained with a mixture of tincture of iodine, 1 part, and absolute alcohol, 4 parts. Only tissues removed and fixed immediately after death are suitable for the demonstration of glycogen, because postmortem it quickly changes into sugar.

Glycogen is found normally in the liver, in the epithelium of the uterus, in the skeletal muscles and the heart muscle, in the blood-serum, in leukocytes, in cartilage cells, and in most of the organs of the embryo. The quantity of glycogen in the liver decreases during starvation.

Under pathologic conditions glycogen is found in certain tumors, such

¹ *Virchow's Archiv*, viii., 1855.

² *Zeits. f. klin. Med.*, vi., 1883.

³ *Virchow's Archiv*, cxx., 1890.

as those of the testicle, bones, cartilages, muscles, in tumors of the kidney from adrenal rests, and of the cervical portion of the uterus. This occurrence of glycogen in tumors is interesting in view of the richness of embryonal tissues in glycogen, and the theory that the tumors spring from embryonal remnants (Cohnheim) would seem to receive some support from this

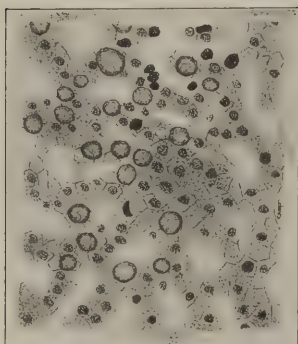


FIG. 30.—Glycogenic infiltration of the liver. $\times 300$.

fact. Glycogen is also found in pus-corpuses; and Czerny observed that the leukocytes give the glycogen reaction in conditions characterized by cachexia.

Glycogenic infiltration is especially marked in diabetes mellitus (Ehrlich). While a large part of the excessive amount of sugar formed in this disease is eliminated in the urine, glycogen is also produced in large quantities, and is found in abnormal amount in the leukocytes and the plasma of the blood, in the liver (Fig. 30), in the kidneys, especially in the epithelial cells lining the loops of Henle, and elsewhere. Experimental diabetes produced by extirpation of the pancreas (Minkowski) has been shown by Trambusti¹ to be followed by a marked glycogenic infiltration of the kidney, liver, and the leukocytes.

Fatty Infiltration; Lipomatosis.—Normally fat is found in various parts of the body, being stored in the cells pending the need of the organism for the potential energy the fat contains, and which, when required, is liberated by oxidation of the fat. The quantity of fat in storage will vary according to the amount of fat produced in the processes of nutrition and metabolism, and the amount consumed in the processes of katabolism. The fat represents in part fat brought as such into the body in the food, emulsified and absorbed in the chyme, and carried by the blood, either in solution or suspended as fine particles, to the storage depots in the cells; in part it represents fat produced by cellular activity from the albuminous and carbohydrate constituents of the food. When an excessive amount of fat is produced, or when the quantity consumed is exceedingly small, or when both of these contingencies concur, a superabundance of fat results, which, if it passes beyond certain limits, becomes abnormal, and conditions develop that are known as obesity, adiposity, polysarcia, or lipomatosis.

The processes that lead to these conditions are referred to as fatty infiltration, and are of a different nature from those concerned in other fatty changes.

As already indicated, fatty infiltration occurs in obedience to the same general laws that govern the physiologic storage of fat, the difference being largely one of degree. Thus, an excessive amount of fat may be produced when the diet contains, in addition to the usual amount of proteids and carbohydrates, an inordinate amount of fat; some of the fat is then, in all probability, simply absorbed from the digestive tract and carried in solution or suspension in the blood to the places of deposit. Or, as is more likely, stored fat results from metabolism of the proteids and carbohydrates, while the fat in the food is immediately oxidized. In this latter case the cell acts

¹ *Centralb. f. allg. Path. u. path. Anat.*, iii., 1892.

as a retort in which the albuminous and starchy substances are converted into fat. The fat is, however, not produced at the expense of the protoplasm of the cell itself, but only from substances brought to it.

In addition to the storage of fat through excessive production from the food, certain conditions that lead to diminished consumption of fat are to be considered. Here are included all those states characterized by lessened labor on the part of the cells, such as absence of muscular activity, sluggish respiration, and chronic anemia, leading to a scant supply of oxygen.

Then there are conditions in which, with a normal supply of food, the constituents of the diet being correctly balanced, and in which the general processes of oxidation seem to be at par, there is, nevertheless, an excessive local or general accumulation of fat. Such conditions depend upon anomalous metabolic processes of unknown origin, the tendency to which may be acquired or inherited. These states seem to depend to a certain extent upon a local or general diminution in the energy or activity of the cells (Cohnheim). The progressive character of the disturbed metabolism is often marked. Among the instances in which this tendency to excessive fatty deposition



FIG. 31.—Fatty infiltration of heart muscle. The fat is stained orange with sudan III. The muscle fibers are compressed.

seems to be acquired may be mentioned the obesity of eunuchs, and of women after premature or natural menopause.

From these general etiologic considerations it becomes possible to define fatty infiltration as the storing of fat in the protoplasm of cells without any essential change in their structure, the fat being in part due to increased formation by the cells, in part to increased supply.

Fatty infiltration may be *general* in the form of a general obesity or universal lipomatosis. Here the increased deposition of fat occurs first in the subcutaneous and subserous connective tissue, in the liver, and in bone-marrow—places where fat is normally stored, and then in places where fat does not occur under normal conditions, namely, in the intermuscular connective tissue of the heart (Fig. 31) and the skeletal muscles, in some cases in submucous connective tissue and elsewhere. In these cases there is often a very marked individual predisposition.

A *local*, circumscribed lipomatosis also occurs. This is commonly seen as a marked increase of fat around atrophic organs or organs diminished in size from other causes; as, for instance, around contracted kidneys and

between the narrow fibers of the atrophic heart, and in the skeletal muscles in the disease known as pseudohypertrophic muscular paralysis. Particularly in the latter it would seem that peculiarities in cellular activity form the predisposing causes for the excessive deposition of fat, which here exceeds the mere filling up of the space left by the atrophic muscle fibers. In connection with this, reference may be made to the so-called multiple symmetric lipomas—multiple, circumscribed, symmetrically disposed, fatty overgrowths—the development of which must be ascribed to peculiarities in cellular activity.

Functional disturbances may result from fatty infiltration, as, for example, in the case of the liver, and particularly of the heart, where the deposition of fat between the muscle fibers may result in muscular insufficiency, and even in rupture of the wall when the latter has become so infiltrated with fat that it no longer possesses the necessary degree of resistance to the intracardiac pressure. An excessive universal lipomatosis may also reach such an enormous extent as to interfere with the movement of the body and with the performance of other functions. In some of the cases of great obesity the thyroid gland has been found diseased.

As stated in the definition of fatty infiltration, there is an absence of all structural changes in the affected cells other than those due to the mere presence of the fat. In the liver cells the beginning of fatty infiltration is signalized by the presence of numerous small fat drops, but there is no marked disturbance in the protoplasm of the cell. Later on, the droplets coalesce to form larger globules, so that in advanced cases the protoplasm forms a capsule for the fat globule, and in this membrane the nucleus will be found crowded to one side, giving rise to the so-called seal-ring appearance (Fig. 32). In

the connective-tissue cells the fat also appears as small drops which rapidly coalesce, so that a large globule is formed, which presses the nucleus to one side.



FIG. 32.—Fatty infiltration of the liver. Large fat globules occupy the liver cells and crowd the nuclei to one side. $\times 125$.

The differential microscopic diagnosis of fatty infiltration and other fatty processes rests essentially upon the presence in the cells, in the latter case, of changes that are indicative of disintegration of the protoplasm (page 97); whereas the cell of fatty infiltration is normal except for the presence of fat. Usually the infiltrated fat occurs in much larger drops than fat under other circumstances, but not invariably. The occurrence of fat in places in which it is not found normally, as, for instance, in the

muscular fibers of the heart or skeletal muscles, in glia cells, etc., speaks in favor of more deep-seated changes. When the fatty infiltration recedes, then the large fat globules become smaller and divide into minute droplets that are gradually removed, so that the cells again present their usual appearance.

In the connective tissue and the bone-marrow disappearance of the fat, both after excessive infiltration as well as under normal conditions, may be followed by the infiltration of serum into the tissue, which becomes jelly-like and translucent, a condition described as serous atrophy of adipose tissue.

Pathologic Pigmentation.—Abnormal pigmentation of tissues may occur in various ways. It may be due to an excessive pathologic formation of the pigment normally found in the skin and elsewhere—*autochthonous* or *metabolic pigmentation*; or it may follow changes in the hemoglobin of the red blood-corpuscles—*hematogenous pigmentation*; or it may be due to absorption of the pigment found in the secretion of the liver, the bile—*biliary pigmentation*, icterus, or jaundice. Finally the pigment particles may be imported into the body from without by inhalation through the lungs, through wounds (as in tattooing), or by introduction into the stomach.

Pigmentation as a whole includes many different and complex processes. In some cases the pigment is the product of increased cellular activity, and the pigmentation bears the stamp of a progressive rather than a regressive disturbance, as, for instance, in the formation of pigment in melanotic tumors. A number of pigments are produced by physiologic as well as pathologic changes in the hemoglobin of the blood. The biliary pigment is a physiologic derivative of hemoglobin; and biliary pigmentation, or jaundice, usually depends upon mechanic obstruction to the outflow of the bile, although in some instances the process is different and more complex. The so-called hematogenous pigments are due to pathologic changes in the red blood-corpuscles, and the pigmentation with these substances is usually a part of secondary absorptive and eliminative processes. Pigmentation with pigment introduced from without is a pure infiltration.

Metabolic Pigmentation.—Pigment normally occurs in various parts of the body in the form of yellowish, brown, or black granules, lying chiefly in the cells, but also in the intercellular substance. Such pigment is found in the deeper layers of the rete Malpighii of the skin, in the epithelium of the retina, in the hair, and in the ganglion cells of the nervous system. Furthermore, pigment is found in the connective tissue of the pia mater, in the choroid and sclerotic coats of the eye, in the muscle cells of the heart, in the adrenals, the testicles, the kidneys, the liver, and in the smooth muscle fibers of the small intestine of older persons. The iron reaction of the pigment in the liver and the testicles speaks in favor of its hematogenous origin. These pigments are called by various names, such as melanin, lipochrome, and hemofuscin.

This normal pigmentation may increase under various physiologic and morbid conditions. The pigmentation in the skin is usually greatly increased during pregnancy; the formation known as freckles is also due to localized increase of pigmentation in the skin. In Addison's disease an excessive pigmentation of the skin develops, due to increase of the normal pigment (Fig. 33, B). A marked increase in the pigmentation of the ganglion cells is usually regarded as of pathologic import. The greatest degree of pigment formation occurs in the so-called pigment moles of the skin and in melanotic tumors.

In the last-named growths the cells (Fig. 33, A) may be diffusely pigmented with brownish or blackish granules, which also lie in the intercellular substance, so that the growth may be entirely black, and the fluid that exudes as black as ink. The urine in these cases may contain substances which on exposure to the air become changed into black pigment particles (melanuria).

The yellowish, brownish, or black granular pigment found under the various conditions mentioned is usually regarded as the product of a special

cellular activity. As regards the skin, Kölliker believes that the pigment is brought by wandering connective-tissue cells—*chromatophores*—which send processes between and even into the epithelial cells, and that in this manner transfer of pigment is accomplished. Karg transplanted a piece of white skin upon an ulcer of the leg of a negro, and found that the originally white skin became black, due to the appearance of pigmented connective-tissue cells between the epithelial cells and the transfer of the pigment to the latter. The origin of the pigment-carrying wandering cells is obscure. Concerning the exact manner of formation of the pigment in other places nothing definite is known. Nor is it known from what material the pigment is formed; whether from the coloring-matter of the blood—which does not

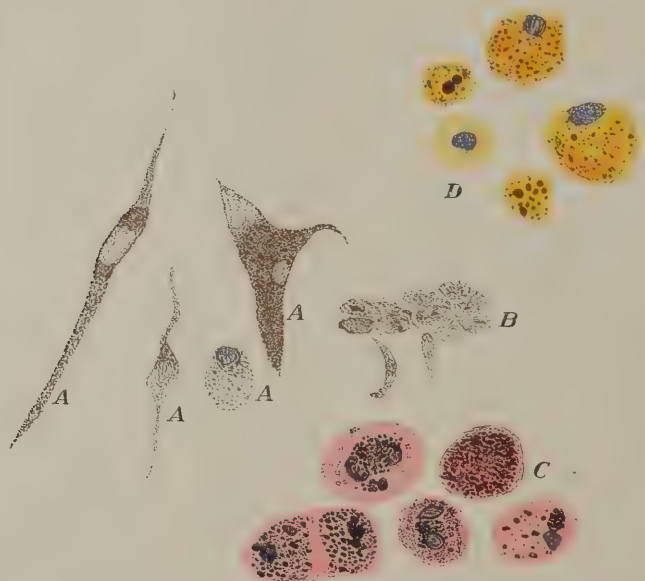


FIG. 33.—Various kinds of pigmented cells: *A*, cells containing melanin, from a melanosaarcoma of the choroid; *B*, pigmented cells from the skin in Addison's disease; *C*, cells filled with coal-dust in the alveoli of the lung; *D*, cells containing changed red cells and blood pigment in lung the seat of passive congestion. $\times 650$.

seem likely, because there is nothing to indicate its formation in the vicinity of the blood-vessels—or from albuminous substances. The large amount of sulphur in some of these pigments (von Nenski)¹ favors the view that it is elaborated by the cells from albuminous material.

Certain pigments of a different composition and of obscure origin are found in the corpus luteum of the ovary in the form of a yellow pigmented fat, called lutein, and in certain rare lymphomatous tumors, called chloroma, on account of their presenting a more or less distinct green color, which also seems to depend upon the presence of a pigmented fat; the yellow formations in the skin known as xanthoma also contain a granular pigment that belongs to the lipochromes. Virchow, and later Böstrom, Hansemann,

¹ *Arch. f. exp. Path.*, xx., 1886.

and Heile,¹ have each described cases in which all the cartilages of the body, as well as other structures, were black, due to the presence of a brownish or black iron-free pigment. This condition is known as *ochronosis*; its cause is not known. Formalin, according to Heile, produces a similar pigmentation of cartilage. Von Recklinghausen regards the yellow iron-free pigment (hemofuscin) of the smooth muscle fibers of the small intestine, seen especially in drinkers, and of other muscular organs, as a derivative of hemoglobin.

Absence of pigment may be congenital; it may be universal (*albinismus universalis*) or partial (*albinismus partialis*). Acquired absence of pigment is discussed in the part devoted to the Pathologic Anatomy of the Skin.

Hematogenous Pigmentation.—This form of pigmentation depends upon the deposition in the tissues of pigment derived from hemoglobin. It occurs either as a secondary process after hemorrhages and thrombosis, or as the result of solution of hemoglobin in the blood-plasma and the formation of granular pigment in the circulating blood.

In the first instance the pigmentation is the result of physical and chemical changes in the hemoglobin, incidental to the absorption and removal of disintegrating red blood-corpuscles and other detritus. The various changes in the color of cutaneous extravasations, as, for instance, in a "black eye," which becomes brown, bluish-green, and yellow before all traces disappear, are the external indications of the various stages in the process of absorption. Similar color changes are observed in connection with the absorption of internal hemorrhages, as in the brain.

After an extravasation of blood the red blood-corpuscles undergo the following changes: A part is returned to the circulation unaltered, by way of the lymphatics; another part loses its hemoglobin, which is dissolved by the serum and diffused throughout the tissues, which it stains brownish or reddish, while the albuminous stroma of the red cells falls to pieces; a third part of the red corpuscles disintegrates, while still containing hemoglobin, into brownish or reddish particles or fragments. Some of the dissolved hemoglobin is absorbed and eliminated in the urine as methemoglobin or urobilin; the remainder of free hemoglobin, as well as that contained in the disintegrating red corpuscles, undergoes further chemical changes whereby it is converted partly into hematin, partly into hemosiderin.

In tissues hardened in alcohol for microscopic purposes the hemoglobin in extravasations may form long, red, splinter-like crystals. These crystals are composed of parahemoglobin, an insoluble form of hemoglobin which develops under the influence of alcohol.

Hematin is a pigment derived from hemoglobin, and occurs either in the form of yellowish or brownish granular masses, or as brick-red rhombic or needle-shaped crystals. It is nearly, if not quite, identical in chemical composition with bilirubin, and responds to Gmelin's test (Virchow); it does not contain iron, and is insoluble in water, ether, and alcohol, but soluble in chloroform and alkaline fluids. It is formed more especially in large extravasations and in hemorrhages into preformed cavities, where the blood is not so much exposed to the action of living cells (Quincke)² and where there is a lack of oxygen (Thoma and Panski).³

¹ Virchow's Archiv, clx., 1900.

² Deutsch. Arch. f. klin. Med., 25, 27, and 33.

³ Arch. f. exp. Path., xxxi., 1893.

Hemosiderin appears in yellowish-brown or brown granules and granular heaps, which are usually enclosed in cells (Fig. 34), but may lie free in the tissue-spaces. It is insoluble in water, and contains iron. If a microscopic section containing hemosiderin is treated with a solution of potassium ferro-

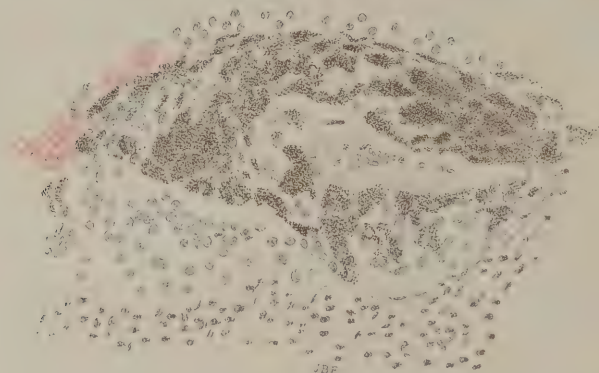


FIG. 34.—Hemorrhagic cyst in the pineal gland. There are masses of brownish granular pigment, and many cells are filled with this material (hemosiderin). To the left are some unchanged red cells. Hematoxylin and eosin. $\times 125$.

cyanid and hydrochloric acid, the hemosiderin granules are stained blue, owing to the formation of Prussian blue (Fig. 35); under the influence of ammonium sulphid or hydrogen sulphid the granules become black, on account of the formation of ferrous sulphid.



FIG. 35.—Masses of hemosiderin in the thickened endocardium beneath an old thrombus. The blue iron reaction was obtained by treating the sections with potassium ferrocyanid and hydrochloric acid. $\times 125$.

Hemosiderin is formed when the extravasated blood is exposed to the action of living cells and of oxygen. The pigment is consequently found by preference in smaller extravasations and at the periphery of larger ones, in small thrombi, and in chronic passive hyperemia of the lungs and other organs, accompanied with hemorrhage by diapedesis. The section

from which the drawing reproduced in Fig. 35 was made came from the wall of a right ventricle, upon the endocardium of which an old thrombus was situated.

While these changes are taking place in the dissolved hemoglobin, as well as in that attached to fragments of red blood-corpuscles, the so-called pigment-carrier cells (Fig. 33, *D*) are transporting the fragments and detritus to the surrounding tissues, and by way of the lymphatics into the regional lymph-glands, which become more or less pigmented. These carrying cells are chiefly leukocytes which have taken up into their interior not only hemosiderin and hematoidin granules, but also fragments of or entire red blood-corpuscles, the pigment of which may undergo further changes in the interior of the carrier cells. The protoplasm of these cells may be stained a diffuse yellow by the dissolved hemoglobin. In this way the changes of color in the vicinity of extravasations and in the extravasated blood itself are explained; as hemosiderin and hematoidin are formed the color becomes more yellowish. Hematoidin may to a certain extent be dissolved by the alkaline fluids, and hemosiderin is probably also gradually destroyed or removed; it may lose its iron, and may be changed to a colorless substance. Hematoidin entering the blood is secreted by the liver as bilirubin, with which it is said to be identical in composition; it is finally eliminated by the kidneys as urobilin.

Pathologic hematogenous pigmentation also occurs after the extensive destruction of red corpuscles in the circulating blood and the setting free of hemoglobin in the plasma. Pigmentation of the internal organs (liver, spleen, marrow of bones) due to the deposition of hemosiderin—*hemosiderosis*—undoubtedly occurs to a limited extent physiologically as red blood-corpuscles gradually wear out and are destroyed.

Excessive destruction of the red cells in the blood occurs in septic infections, grave malarial fever, pernicious anemia, and in many forms of intoxication, as, for instance, with potassium chlorate, poisonous fungi, toluenediamin, etc.; in the disease known as periodic hemoglobinuria, and after the introduction of the blood of one animal into the body of another of a different species. The general results that may follow such excessive disintegration of red blood-cells are: *hemoglobinemia*—i. e., a discoloration of the plasma by the hemoglobin in solution; *hemoglobinuria*, or *methemoglobinuria*, when the dissolved hemoglobin is eliminated in the urine, which then becomes brownish-red or dark red in color; increase in the amount of pigment in the bile; and pigmentation of various internal organs by pigments derived from hemoglobin, especially by hemosiderin.

The degree of the pigmentation of the internal organs depends upon the relation of the pigment set free in the blood to the capacity of the liver to convert it into biliary coloring-matter. If the liver is not able to utilize, in the formation of biliary pigments, all the blood-pigment brought to it, then the derivatives of the hemoglobin are deposited in various internal organs, and to a certain extent are excreted in the urine. The pigmentation produced in this manner is due chiefly to the deposition of hemosiderin; the iron-free hematoidin does not seem to be produced to any great extent, or, if so, it is largely utilized by the liver (bilirubin). The iron-containing pigment is deposited in the form of yellow or brown granules or flakes in the liver, spleen, bone-marrow, lymph-glands, and kidneys. The pigment particles are brought to the organs in question either free or enclosed in leuko-

cytes; thence they are taken up by the endothelial cells of the capillaries and passed into the cells proper of the organs. In pernicious anemia and in malaria the pigmentary infiltration of the liver cells may be so great as to give the organ a yellowish-brown, orange, or bluish color, which is best marked in the periportal connective tissue and in the periphery of the acini. In the lymph-glands the particles are found especially in the free cells; in the spleen the free as well as the fixed cells may become pigmented; and in the bone-marrow the pigment is partly enclosed in cells lying in the capillaries, partly in the endothelial cells, and also in the marrow cells proper. In the kidneys the pigment particles are to be found in the endothelial cells, the epithelium of the convoluted tubules, and in the lumen of the tubules. In malaria, in addition to the hemosiderin produced by the disintegration of the red cells, the parasites elaborate a black iron-free pigment, which is deposited in various organs, and is the essential cause of the melanosis or

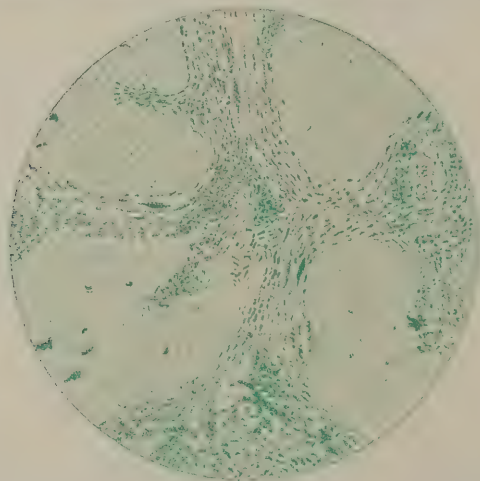


FIG. 36.—Hemochromatosis and cirrhosis of the liver. Iron reaction with potassium ferrocyanid and hydrochloric acid. $\times 100$.

pigmentation of the spleen, liver, bone-marrow, and brain-cortex observed in chronic malaria.

Under the name *hemochromatosis* von Recklinghausen described a general pigmentation with an iron-containing and an iron-free pigment. This form of pigmentation is associated with cirrhosis of the liver and of the pancreas, and at times with diabetes mellitus (the so-called bronzed diabetes) (Fig. 36). The ordinary destruction of red blood-corpuscles does not produce such widespread and general pigmentary deposits.¹

Pseudomelanosis is the term applied to a certain bluish-gray or black discoloration that is found in the peritoneum and the abdominal organs of cadavers. It has been regarded as entirely of postmortem origin, but, according to Neumann, it depends upon local conditions existing during life which favor the development of hemosiderin, the subsequent combination of which with ammonium sulphid gives rise to the discoloration.

¹ See Opie, *Jour. Exper. Med.*, iv., 1899.

The green discoloration that forms along the subcutaneous blood-vessels during decomposition is due to the action of hydrogen sulphid upon methemoglobin.

Biliary Pigmentation.—Icterus, or jaundice, is a general pigmentation of the tissues of the body with the coloring-matters of the bile. The biliary pigments are produced in the liver. This is shown by the facts that neither the blood of the portal vein nor that of the hepatic artery contains any of the constituents of the bile, and that when the liver is removed from geese and ducks no bile is produced (Minkowski and Naunyn). The biliary pigments are derivatives of hemoglobin, and the biliary pigment known as bilirubin is identical with hematin, the iron-free derivative of hemoglobin found in extravasated blood. Under normal conditions the biliary pigments are passed on into the intestines, together with the other constituents of the bile, a part being evacuated with the feces, while another part is absorbed into the blood through the mucous membrane of the intestine (Hoppe-Seyler). When it reaches the blood it has undergone such chemical changes as to elude demonstration, but its presence in the blood in some form is shown by the constant occurrence in the urine of a derivative of bilirubin known as urobilin.

Icterus is produced by the passage of the bile and its coloring-matter from the liver into the lymphatic vessels and the blood. The essential cause of icterus is *obstruction to the outflow of the bile into the intestines*. Among the many conditions that may give rise to biliary obstruction are catarrhal inflammation of the bile-ducts, and the occlusion of the lumen of the biliary papilla in the duodenum by a plug of mucus; narrowing and closure of the biliary passages by impacted calculi, contracting scars, and tumors; fibrous bands causing kinking of the ducts; pressure of enlarged lymph-glands; inflammatory foci, connective-tissue proliferation, and tumors developing in the liver-substance and compressing or obliterating the biliary canals and capillaries so as to prevent the outflow of the bile.

The typical results of such obstruction are the following: No more bile reaches the intestine, the contents of which lose the color due to the bile and become clay-colored; intestinal digestion is disturbed and putrefactive processes develop on account of the absence of bile. The damming of the bile causes dilatation of the biliary ducts and canals, stagnation of their contents, and absorption by the lymphatics of the biliary coloring-matter and acids, which reach the general circulation by way of the thoracic duct; the intercellular biliary capillaries as well as the intracellular passages are distended, and the liver-cells themselves become pigmented because they cannot get rid of the pigment produced in their interior. Excessive dilatation of the biliary capillaries may lead to their rupture and the direct entrance of bile into the circulation (Ziegler). Some authors, as Szubinski,¹ claim that there are two sets of passages in the liver-cells—biliary and vascular—so that the bile is readily absorbed into the blood in stagnation in the intracellular biliary canals. A general staining of the organs and fluids of the body by the biliary coloring-matter present in the blood, either in solution or as granular pigment particles, is produced. During life this is best shown by the yellow or greenish-yellow discoloration of the skin, the conjunctivæ, and the urine; after death the internal organs, the serous mem-

¹ Ziegler's *Beiträge*, xxvi., 1899. See also Nauwerck, *Münch. med. Woch.*, 1897; and Fütterer, *Medicine*, 1897.

branes, the blood-plasma, transudates and exudates that may be present, are all found more or less bile-stained. The solid pigment particles which circulate in the blood, either free or enclosed in leukocytes, are deposited here and there in the body, especially in the lymph-glands, spleen, and bone-marrow. In persistent and excessive icterus many of the tissues may contain bilirubin in solid form, usually as granular particles, rarely in the shape of rhombic and needle-shaped crystals. The kidneys, which eliminate the biliary coloring matter, show pigmentation of the epithelial cells of the uriniferous tubules, and of the casts that are usually present in the tubules in jaundice.

The general functional disturbances characteristic of icterus depend not so much upon the presence of the biliary coloring-matter in the circulation as upon the simultaneous presence of the biliary acids. These acids have the power of destroying the red blood-corpuscles, thus setting free hemoglobin (Leyden,¹ Löwit²). The free hemoglobin increases the formation of bilirubin by the liver, and in this way it may serve to intensify the jaundice at the same time as the iron-containing pigment derived from the hemoglobin—hemosiderin—is deposited in the various internal pigment depots.

The removal of the biliary obstruction is succeeded by a gradual disappearance of the pigmentation. The liver secretes a larger amount of bile, which is to a great extent excreted by the intestines, and as the jaundice disappears the amount of urobilin in the urine is also greatly increased.

More or less well-marked icteric pigmentation is met with in conditions in which the red corpuscles are destroyed in the circulating blood. This occurs in many infections and intoxications; in septicemia, typhoid fever, yellow fever; after the bite of venomous serpents, blood-transfusion, inhalation of chloroform and ether, the administration of toluylendiamin, etc. It was formerly held that in these cases the formation of the biliary pigment, the bilirubin, occurred in the blood, and the jaundice was designated as hematogenous, in distinction from the jaundice produced by biliary obstruction, which was termed hepatogenous. This can no longer be regarded as correct. On removing the liver from geese and ducks, Minkowski and Naunyn found that the production of bile ceased. They then caused extensive destruction of the red corpuscles by allowing the animals to inhale arsenous hydrid; but even then no biliary pigment was formed, showing conclusively that the liver is the seat of production of the biliary coloring matter. It must again be stated, however, that bilirubin, or hematoidin, is formed in blood-clots, and the yellow color that occurs in the process of absorption may be considered a local icterus in so far as the yellow color depends upon the presence of hematoidin; but biliary pigment is never formed outside the liver to the extent that a general jaundice is produced. The so-called toxic or infectious icterus depends upon an increased production of biliary pigment in the liver and the absorption of the bile into the circulation. The causes that determine the absorption of the bile under these circumstances are not clearly understood; it is believed that it may occur from the biliary passages and from the intestines, and that the changes in the consistency of the bile, due to the increased amount of pigment, favor absorption (Stadelmann).³

¹ *Pathologie des Icterus*, 1866.

² *Ziegler's Beiträge*, iv., 1889.

³ *Der Icterus*, 1891.

Another circumstance that shows toxic or infectious icterus to be hepato-genous is the fact that the urine and the blood may contain biliary acids.

An excessive destruction of red blood-corpuscles in the circulating blood under toxic or infectious influences results, then, in an increased formation of bilirubin by the liver from the liberated hemoglobin, which may be absorbed into the circulation and give rise to jaundice, while the derivatives of hemoglobin retained in the organs consist almost entirely of hemosiderin.

The so-called *icterus neonatorum*, or jaundice of the newborn, has been explained in a variety of ways. In many cases it is due to obstruction of the biliary ducts. Thus, in hereditary syphilis Gerhardt and Somer found the jaundice to be dependent on connective-tissue growth around the bile-passages, which were compressed. In another group of cases the jaundice has an infectious basis, due to septicopemic processes.

In a large number of instances, however, jaundice develops in healthy children during the first few days after birth. This is *icterus neonatorum* in the strict sense. Frerichs¹ explained it as due to a fall of pressure in the capillaries of the liver, which resulted in an entrance of bile into the blood. Others have advanced the view that the increased destruction of red blood-corpuscles causes an excessive production of bilirubin, which is absorbed. Hewitt and Silbermann regard the icterus as dependent upon an increased destruction of red corpuscles and upon biliary obstruction due to compression of the bile-capillaries by the dilatation of the blood-vessels of the liver that occurs after birth. Birch-Hirschfeld² regards the jaundice as due to compression of the biliary capillaries and passages by Glisson's capsule, which follows the venous congestion that at times occurs during and after birth. The resulting edema of Glisson's capsule, which is often demonstrable, develops especially after protracted labor, in cases of twists of the umbilical cord, and in insufficient heart action. Ziegler believes that the jaundice depends upon resorption of the biliary pigment, which is not only produced in large quantities in the liver, but is also absorbed in large amount from the meconium and carried back to the liver.

The jaundice of the newborn is characterized not only by a diffuse yellow pigmentation of the tissues, but also by the deposit of bilirubin in adipose and connective tissue.

Imported, or External, Pigment.—Pigmentation of external origin may take place:

a. Through the skin; and here most frequently as the result of tattooing. This practice consists of puncturing the skin with a sharp instrument and then rubbing in various insoluble, granular coloring matters, such as India ink, charcoal, cinnabar, etc. A part of the material remains in the small cicatrices that form, while some is carried by the lymphatics to the regional lymph-glands, which also become pigmented.

A similar traumatic pigmentation of the skin of the face and elsewhere occurs after explosions of gunpowder, leading to the formation of powder-marks; also in coal-miners from the entrance of coal-dust into the skin. A permanent local pigmentation of the skin occurs in workers with silver.

b. Through the Alimentary Canal.—The only important form of pigmentation due to introduction by way of the stomach is pigmentation by silver—*argyrosis*, or *argyria*. When preparations of silver are administered for a

¹ *Leberkrankheiten*, i., 1858.

² *Virchow's Archiv*, lxxxvii., 1882.

long time the silver is absorbed into the circulation, presumably as an albuminate, and is deposited in the form of black or brown granules in various tissues, which become uniformly dark gray in color. The deposition takes place chiefly in the skin; in the kidneys, where it is deposited in the intercellular substance of the glomeruli and the medullary pyramids; in the arterial intima, the serous membranes, the choroid plexuses of the brain,¹ etc. The blue line along the gums in lead-poisoning (saturnism) is due to the ingestion of lead with the food.

c. *By Inhalation.*—The lung is the most frequent seat of pigmentation. Finely divided dust carried into the lungs in inspiration is in part retained. The most frequent pigment thus introduced is coal-dust. Residents of large cities, as well as miners and workers in coal, always present more or less coal-dust pigmentation, or anthracosis, of the lungs, and not infrequently this reaches such a degree that the organ becomes perfectly black. The coal-dust is at first free in the alveoli or enclosed in leukocytes and alveolar epithelial cells (dust-cells or carrier-cells) (Fig. 33, C). Later it is also found in the alveolar septa, and in the interlobular, perivascular, and peribronchial connect-

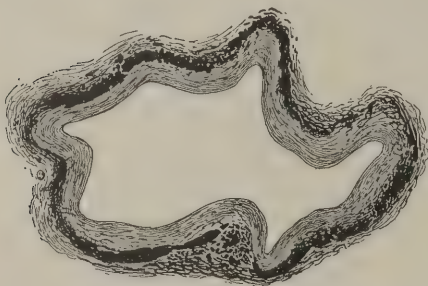


FIG. 37.—Masses of coal-dust in perivascular lymph-spaces of a pulmonary vein. $\times 75$.

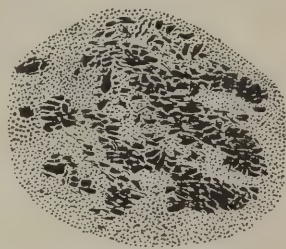


FIG. 38.—Coal-dust in peribronchial lymph-node. $\times 75$.

ive tissue, where the granules are deposited in compact masses (Fig. 37). From the lungs the pigment is carried by the lymph-current to the peribronchial lymph-glands (Fig. 38), which may become black throughout and considerably enlarged. On account of the mechanic irritation produced by the pigment connective-tissue proliferation may take place, resulting in the formation of a great deal of hard, fibrous tissue about the bronchi and blood-vessels, and between the lobules. When inflammatory or tuberculous foci are replaced by connective tissue this may become completely infiltrated with coal-dust, giving rise to black areas of induration. According to some authorities, however, the inflammatory changes following the inhalation of coal-dust are due to bacteria attached to the dust rather than to the mechanic action of the latter.

From the lungs the coal-dust may reach the general circulation, either directly by being deposited throughout the entire thickness of the walls of the vessels and thus becoming mixed with the blood (Arnold), or by the softening of anthracotic peribronchial lymph-glands and secondary involvement of the walls of the large veins in their neighborhood (Weigert).² The intima of these large veins often shows pigmentation. The coal-dust

¹ Von Kahlen, *Ziegler's Beiträge*, iv., 1894.

² *Fortschritte d. Med.*, 1883.

might also reach the general circulation by way of the lymphatics after passing the glandular filters, or by retrograde transport along mediastinal lymph-currents running in reversed direction to the normal. Coal-dust that has reached the general circulation is deposited in the liver, spleen, or bone-marrow, and an instance has been described by Welch in which it infiltrated the liver to such an extent as to be regarded as the cause of the cirrhosis that existed.

Iron workers and polishers occasionally present a reddish pigmentation of the lung, due to the inhalation of powdered oxid of iron; this is known as *siderosis* of the lung. *Chalcosis* and *silicosis* result from the inhalation of marble-dust¹ and quartz-dust respectively.

The Petrifying Infiltrations and the Formation of Calculi.—Petrifying infiltration is due to the deposition in the tissues of certain solid, crystalline, amorphous, or granular salts, which are either salts of lime or salts of uric acid. When the former are deposited the process is known as *calcareous infiltration*, or *calcification*.

Calcification is due to the precipitation in the tissues of granular particles and masses of the phosphates and carbonates of lime and magnesium. It takes place as a physiologic process in the calcification of osteoid tissue during the process of ossification of the skeleton; here calcification occurs as an essential step in the formation of the new tissue. With the further exception of the calcification in tumors that produce bone, all other instances of calcareous infiltration in the body must be regarded as retrogressive changes, because no new tissue is formed, but old tissue is petrified.

Pathologic calcification, or petrification, occurs almost without exception only in degenerating, dying, or dead tissue.

In old age calcification of the costal cartilages, of the cartilages of the larynx, and of the walls of arteries takes place with great constancy; it is believed to be due to an excessive quantity of lime salts dissolved in the blood in consequence of senile involutionary changes and processes of absorption in the bones. In this form of calcification, which is so constant as almost to be physiologic, the lime salts are deposited in the arterial walls and in the disintegrating intercellular substance of the cartilages—the antecedent retrogressive changes in these being also of constant occurrence in old age. It may occasionally happen that the increased resorption of lime salts leads to calcification of apparently normal tissue, such as the lungs, the kidneys, and the mucous membrane of the stomach. The resorption of lime salts from one tissue and their deposition in another are referred to as lime metastasis,² or metastatic calcification (Virchow).

While metastatic calcification is of frequent, almost constant, occurrence in old age, calcification of dead or dying tissue is also very often observed in early life, when the source of the lime salts must be sought in the food rather than in processes of reabsorption.

Calcification occurs very often in connective tissue the seat of sclerosis and hyaline degeneration, as, for instance, in the blood-vessels in arterio-sclerosis, in hyaline degeneration of small cerebral vessels, in the heart-valves in endocarditis, in chronic inflammatory thickenings in the pleura and pericardium, and in the thyroid gland. It also takes place in foci of

¹ Betts, *Jour. Am. Med. Assoc.*, xxxiv., 1900.

² Some writers object to this use of the word metastasis, the term really implying a transfer of disease.

fatty degenerations in the arterial walls, and in various tumors, as fibromyoma of the uterus, in all kinds of necrotic areas due to caseation or coagulation-necrosis, in inspissated pus and inflammatory exudates, in the capsules of animal parasites (trichina), in thrombi (phleboliths), and in dead fetuses retained in the peritoneal or uterine cavity (lithopedion). Calcareous infiltration also takes place in dead ganglion-cells of the brain in shock, softening, and other nervous diseases (Friedländer), and in the renal epithelium after necrosis following anemia (Litten, Israel), or in that caused by various forms of intoxication, such as with corrosive sublimate (Kaufmann) and with aloin (Gottschalk).

The exact chemical reactions of calcification are not known. In general it would seem to depend upon the precipitation of insoluble or very slightly soluble calcareous salts in organic substances that have great affinity for lime; and we may conclude, in view of the fact that necrotic foci nearly always become calcified, that calcification of degenerated or dead tissue occurs, as a general rule, when the blood contains an abundant amount of lime salts.

Calcareous infiltration produces more or less firm, whitish areas; at times compact masses of stony hardness are formed. In some places calcification results in the formation of round or oval concretions. Such concretions occur normally, in the form of laminated globular masses, in the pineal gland and in the plexuses of the cerebral ventricles, forming the so-called brain-sand (*acervulus cerebri*). They may occur in the cerebral membranes, in various tumors of these structures (*psammoma*), and also in caseous foci and hyaline connective tissue. The formation of such concretions depends upon the calcification of necrotic cells and intercellular substance.

Microscopically calcareous tissue may be recognized by the presence of fine, refractile granules in the intercellular substance or in the cells. These granules are dark in transmitted, white in reflected, light. Calcification in structureless necrotic masses gives rise to the formation of roundish and irregular granules, and occasionally to more homogeneous masses. Upon the addition of strong hydrochloric or nitric acid to calcareous material effervescence takes place, carbonic-acid gas being liberated in the form of bubbles. Tissues the seat of calcareous infiltration differ from normal tissue in their behavior to certain stains, inasmuch as they stain a diffuse bluish-violet with hematoxylin and red with picrocarmin.

A deposition in the tissues of the salts of *uric acid* occurs in the disease known as gout, which is characterized by a general disturbance of metabolism, in consequence of which an excessive amount of uric acid is formed and deposited in various parts of the body.

The infiltration affects by preference the articular cartilages and ligaments, the tendons and tendon-sheaths, the kidneys, the subcutaneous tissue, the auricular cartilages, etc. The favorite seat for the deposit is the metatarsophalangeal joint of the big toe, where it occurs during the acute attack of gout. The material deposited consists of the salts of uric acid, especially sodium urate, accompanied by smaller amounts of phosphate and carbonate of lime. The sodium urate appears in the form of sheaves of fine, needle-shaped crystals, which are first deposited in the intercellular substance of the cartilages, the cells of which are at first unchanged. As the infiltration increases the cartilage becomes opaque and dark in transmitted light; soon extensive necrosis occurs in the infiltrated tissue, followed by the characteristic articular changes that are considered elsewhere.

In chronic cases uric-acid salts may be deposited in a great number of places in the body in the form of circumscribed masses, called tophi.

Calculi, or stones, are formed by the precipitation of solid substances from the fluids of the body. Calculi occur in the ducts of glands and in cavities lined with mucous membrane. The concretions found in blood-vessels, and due to calcification of thrombi, and in the tissue-spaces, such as the brain-sand already referred to, are, strictly speaking, also calculi. In the main all calculi consist of an organic or albuminous ground-substance, upon which a crystalline or granular material is precipitated. A great number of substances may act as the matrices or nuclei of calculi, such as desquamated cells, flakes of mucus, fibrinous masses, exudates, colloid substance, bacteria, and foreign bodies; around and in such bodies are then deposited crystalline or granular precipitates of varying chemical composition, depending upon the place of formation and the nature of the fluids in question.

Obstruction to and delay in the excretion of fluids, such as urine, bile, etc., accompanied by chemical changes in their composition, due to local or general causes, are the essential conditions which, in the presence of an organic matrix, lead to the formation of calculi.

The following are the more important calculi:

Biliary Calculi (Gall-stones).—Gall-stones are among the most frequent calculi. They occur oftenest after middle life, and after the sixteenth year they are found in 25 per cent. of all bodies. They are from two to four times as frequent in women as in men, a fact which is usually explained as due to a greater liability to biliary obstruction and catarrhal inflammation of the bile-passages in women on account of lacing and pregnancy, desquamated epithelium forming the necessary matrix for the deposition of precipitates from the bile. It has also been shown that bacteria (*B. coli*, *B. typhosus*, *staphylococcus*, and *streptococcus*) occur in the gall-bladder, where they may live for a remarkably long time. The occurrence of agglutination of the typhoid bacillus in the bile has been demonstrated, and various bacteria have been found in the center of gall-stones. Gall-stones have also been produced experimentally by injecting bacteria into the gall-bladder of animals.¹

Catarrhal cholangitis leads to epithelial desquamation and albuminous exudation; the bile becomes albuminous, and a compound of bilirubin and albumin is precipitated. Around this nucleus are then deposited various salts and other solid substances, their exact nature and ratio of admixture depending upon the composition of the bile. Naunyn has shown that cholesterin and lime salts are largely produced by the mucous membrane of the gall-bladder, especially when the latter is the seat of catarrhal inflammation induced by bacteria (lithogenous catarrh).

According to their composition, biliary calculi are divided into cholesterin, cholesterin-pigment, biliary-pigment, and carbonate-of-calcium calculi. The most frequent are the first two, which have a crystalline fracture surface often showing lamination. The color varies according to the amount of pigment; pure cholesterin calculi (rare) are practically colorless. The size and number vary greatly. When more than one calculus is present facets are usually formed on the stones, in consequence of mutual apposition.

The pigment calculi are usually small, irregular, crumbling masses, which often form in great numbers in cases of biliary obstruction.

¹ For references to literature, see Cushing, *Bull. Johns Hopkins Hosp.*, ix., 1898.

Urinary Calculi.—Obstruction to the urinary outflow favors the formation of stones, as it brings about changes in the stagnating urine that lead to the precipitation of various salts; it also induces alterations in the epithelium of the urinary tract, so that it may furnish the matrix for the formation of the stone; and it may further lead to infection of the urine, which in turn causes changes in the urine and the mucous-membrane.

General disturbances of metabolism also play a very important part, because they may lead to an overloading of the urine with substances that are easily precipitated, such as uric acid in gout, and that may cause necrosis of the epithelial lining. The albuminous organic matrix which is found in urinary calculi plays a decisive role in their formation; and it has been shown by Ebstein,¹ Naunyn, and others that such albuminous substances have the power to cause a precipitation of crystalline bodies from their solutions.

The composition of urinary calculi varies, depending on the one hand upon the composition of the urine as determined by the general metabolic processes in the body, and on the other hand upon changes in its composition, after its secretion by the kidney, due to bacterial and fermentative processes.

Urinary calculi usually manifest a gradual growth; the varying composition of the urine and the development of fermentation in the latter may serve to give the calculus a mixed composition; the conditions may be such as to lead to the formation in the same person of urinary calculi of different composition.

In the tubules of the kidney minute granules may form in poisoning with corrosive sublimate and other substances, the result of calcification of necrotic epithelial cells. In gout uric acid is frequently precipitated in the uriniferous tubules; while in the newborn the so-called uric-acid infarction (an unfortunate term) of the medullary pyramids of the kidney is often observed. It is due to the precipitation in the collecting tubules of uric-



FIG. 39.—Coral-shaped calculus in the pelvis of the kidney.

acid salts in the form of small yellowish masses, apparently embedded in an albuminous stroma, and giving the pyramids a yellowish or reddish striation. Uric-acid infarction occurs during the first two weeks of life, sometimes in fetal life, and is looked upon as being due to a metabolic disorder. Occasionally it gives rise to hemorrhage from the kidney.

Urinary calculi may occur in the tubules of the kidney, the pelvis of the kidney, the ureter, the bladder, and the urethra.

They present themselves as minute particles, known as sand or gravel, as rounded, smooth or rough, faceted stones of varying size and consistence; or as branching, coral-shaped casts of the pelvis and its calyces (Fig. 39). The following are the principal forms:

(a) *Uric-acid calculi*, composed of either uric acid or urates; (b) *phosphatic calculi*, composed of phosphate of calcium and phosphates of ammonium and magnesium; (c) *calcium-carbonate calculi*; (d) *calcium-oxalate calculi*; (e) *cystin calculi*; (f) *xanthin calculi*.

Fecal calculi are composed of layers of inspissated feces and lime salts.

¹ *Die Natur und Behandlung der Harnsteine*, 1884.

Salivary and *pancreatic calculi* are also composed of lime salts infiltrating an albuminous matrix produced by the epithelial lining of the ducts of the glands. The deposits often observed upon the teeth (tartar) are composed of lime salts, mucus, remnants of food, desquamated cells, and bacteria.

The consequences of calculi are discussed in connection with the morbid anatomy of the various organs in which they occur.

CYSTS.

Cysts are secondary consecutive formations that occur in different organs under similar conditions, and consequently merit a more general consideration.

In the broad sense, a cyst is a pathologic cavity provided with a distinct membrane enclosing fluid or semifluid contents. While the significance attached to the word cyst is not exact, yet the distinction between ordinary cysts and cystomas should always be kept in mind. A *cystoma* is a true tumor, arising from active proliferation of a matrix destined to form cystic spaces; whereas a cyst is a secondary formation not primarily due to tissue-proliferation. Cysts may be classified in the following etiologic groups:

Retention Cysts.—These cysts depend upon abnormal dilatation of glandular follicles and ducts, as well as other pre-existing cavities and canals, due to the accumulation of the secretion characteristic of the various structures in question. Retention cysts possess either an epithelial or an endothelial lining. The essential cause of retention cysts is obstruction to the outflow or failure of removal of the secretion that forms the contents of the cyst. The narrowing or closure of the duct of a gland or the outlet of a canal, through a contracting scar, external pressure, torsion of the duct, impaction of stones, foreign bodies, or thickened secretion, is followed by cystic dilatation if secretion still occurs behind the obstruction, and when the secreting parenchyma or membrane does not itself reabsorb the fluid. Such occurrences are frequent in the kidney. On account of the formation of fibrous tissue in its interior, in consequence of chronic interstitial changes, some of the uriniferous tubules become occluded from the pressure of the contracting fibrous tissue. The result is that the secretion dilates the canals and the capsules of the glomeruli into cysts of various sizes, the contents of which, at first clear and thin, may become greatly altered from obscure chemical changes as well as from degeneration in the lining of the cyst.

Further examples of retention cysts due to obstruction and failure of absorption are seen in the dilatations that form in the ducts and follicles of the sebaceous glands (comedo, milium, atheroma), in the mucous glands of the digestive and respiratory tracts, in the uterine glands (ovula Nabothii), in the canals of the epididymis, in the mammary gland, in the pancreatic duct, in the glands that open into the mouth (ranula), and also in larger canals, such as the ureters, the Fallopian tubes, the bile-passages, and the vermiform appendix.

In the case of closed glandular follicles an abnormally abundant or altered secretion or changes in the follicular walls may lead to cystic dilatation from failure of absorption. This variety of retention cysts is seen in the thyroid gland, the hypophysis, and the ovary.

In the instances of retention cysts above alluded to the lining of the cysts is epithelial, because the dilatations occur in structures normally lined

with epithelium. Retention cysts with endothelial lining may develop in lymph-vessels, in bursæ, and tendon-sheaths. Hydrocele, due to accumulation of serum in the tunica vaginalis testis, and cysts in the lymph-spaces of the neck and elsewhere, are examples of retention cysts with endothelial lining; bursæ and synovial sheaths also present cystic conditions the result of inflammation and irritation.

Cysts from Softening.—Cystic cavities with more or less distinct walls, but without either an epithelial or an endothelial lining, occur in a number of organs as the result of retrogressive changes, accompanied by disintegration and softening. Thus in the brain, hemorrhagic as well as anemic softening may be followed by the formation of cysts, due to encapsulation of the liquid or liquefied remainder of the clot or the softened area in a sac of connective tissue. And in many tumors, more especially sarcoma and carcinoma, extensive necrosis, fatty and mucoid degeneration, may give rise to cysts with fluid or semisolid contents.

Tubulo-cysts.—The cystic dilatations which frequently develop in functionless ducts and tubules, present in the body as remnants of embryonal structures, are called tubulo-cysts by Sutton. In these interesting cysts the process is essentially one of dilatation of a small pre-existing space by the gradual accumulation of fluid, produced either by secretion of the lining of the cavity or by transudation of the lymph-vessels and blood-vessels. Tubulo-cysts are therefore essentially retention cysts, differing from ordinary retention cysts in so far as they concern functionless remnants of embryonal structures that have undergone incomplete involution; from cystoma, in that the process of their formation is rather a mechanic dilatation than an active proliferation; and from some teratomas in the simplicity of their structure. In the last instance the difference is one of degree only.

The more detailed consideration of these cysts belongs elsewhere. Here it will suffice to enumerate the more important examples: parovarian, due to dilatation of the tubules of the parovarium or epoophoron (Wolffian tubules); vaginal, in connection with Gärtner's ducts; branchial, due to unobliterated remnants of the branchial clefts; cysts of the thyroglossal and omphalomesenteric or vitelline ducts.

Parasitic cysts, due to the presence in the body of parasites in a cystic or vesicular stage, such as echinococcus cysts (*Tænia echinococcus*), are of such a radically different origin from that of ordinary cysts that their consideration does not properly belong here.

The contents of cysts in general depend, first, upon the tissues in which they develop. Retention cysts may contain cholesterin, colloid material, serum, saliva, milk, sebaceous material, or mucus. Softening cysts may contain serous fluid, mucoid material, fatty detritus, and the remnants of tissue cells and blood-corpuscles. But the appearances and nature of the cystic contents vary and change much. Intracystic hemorrhages may occur; desquamated and degenerated cells and fragments from the lining membrane may become mixed with the fluid. The contents occasionally become inspissated, and then the remaining mass of detritus may undergo infiltration with calcareous particles.

The gradual dilatation of the tubular follicular structures and spaces in which cysts form is in some instances necessarily accompanied by new formation of tissue in the wall, and, in the case of cysts from softening, the wall is often formed by proliferation of the connective tissue, so that

while cysts cannot well be regarded as other than more or less retrogressive, secondary, or mechanic formations, the process need not be degenerative or passive in all its stages. It is also to be recollected that retention cysts often develop in connection with tumors in glandular structures, and it may be difficult or impossible to separate such cysts from the true cystic tumor, the cystoma.

The commoner secondary changes in the cyst-wall are inflammation, as a remote result of which the cavity may become obliterated, and calcification, the common fate of useless, dead, or dying tissue.

THE PROGRESSIVE CHANGES.

Introduction.—The progressive changes are observed in the regeneration of the various tissues after loss of substance by wear, traumatism, or necrosis, and in hypertrophy and hyperplasia. These changes are progressive not only because they are the result of increased cellular activity, but also because they serve to repair and to preserve structure and function, as shown so distinctly in regeneration. On the other hand, the cell proliferation that leads to the growth of tumors serves no such useful purpose.

The essential nature of progressive changes consists in the formation of new cells, and in some cases also in the enlargement of existing cells. The multiplication takes place according to the same laws that govern normal cell division. There is no pathologic type of cell multiplication; at the most, occasional modifications of the normal process may occur. It is therefore not necessary to detail here the phenomena of mitotic division, which is the essential form of multiplication, or of the amitotic, concerning the importance of which the opinions of cytologists still differ. Irregular mitosis, hypermitosis, and other changes in the nuclei in proliferation will be discussed in the section on Tumors.

An increase in the number of cells, called *hyperplasia*, takes place under a variety of circumstances. It occurs in most instances of hypertrophy; in all the forms of regeneration; in tumor growth; as the result of mechanic and chemical irritation; and from causes as yet unknown (leukemia, etc.).

In some cases the proliferation may be diffuse and uniform throughout the whole organ involved; in other cases it may be focal and circumscribed, or it may affect one variety of cells to the exclusion of others. This occurs, for example, in chronic inflammations, in which there may be more or less isolated hyperplasia of the connective tissue.

As will be shown in the study of regeneration of tissues, the different kinds of cells in the body possess an unequal degree of proliferative power. Generally speaking, the younger the individual the greater the faculty of multiplication of the cells. Cells that are highly specialized, as ganglion-cells, bone-corpuscles, and striped-muscle cells, have but little power of proliferation; but surface epithelium, glandular cells, and connective-tissue cells possess marked regenerative powers.

The division of pre-existing cells gives rise to embryonal or formative cells, which by further changes and by the secretion of an intercellular substance form the definitive tissue; the subsequent development follows the same general rules in pathologic as it does in physiologic proliferation.

It is almost universally recognized that a cell gives rise to another cell of the same kind only; *e. g.*, an epithelial cell forms a new epithelial cell, and

not a connective-tissue cell, and a connective-tissue cell a connective-tissue cell. This is the law of the specificity of cells. *Omnis cellula e cellula ejusdem generis.* It is true that the connective tissues—cartilage, bone, myxomatous tissue, and ordinary connective tissue—are able each one to form all the other members of the group; but it is to be remembered that the active proliferation occurs, in each instance, in mesoblastic connective-tissue cells, the difference in the structure of the mature tissues being due to the different intercellular substances produced in each instance. According to Hansemann,¹ this law of specificity, which at the present time is quite generally recognized, at least in the higher animals, is also demonstrated by appreciable differences in the mitoses of the various tissues, the form, size, and number of chromosomes being characteristic for the cells of each particular tissue.

While the real cause of cell division and cell multiplication is not known, yet the essential conditions necessary for cell proliferation have been determined to a considerable extent. Many cells seem to have a constant tendency to proliferation; this is demonstrated, for instance, by the facts learned from transplantation. Transplantation is the bringing of pieces of one tissue into or upon another and securing their growth. It is made possible by the fact that certain cells retain their power of proliferation after they have been removed from their original place of development and growth. Thus, periosteum, bone-marrow, and cartilage have all been transplanted successfully into soft parts and into blood-vessels (Cohnheim and Maas).² It has been found that it is especially young tissue that will grow, and that growth after a time comes to a standstill and may be succeeded by atrophy. This atrophy in the case of transplantation with osteogenetic tissue undoubtedly depends upon disturbances or absence of function. Transplantation of skin was shown by the researches of Reverdin and Thiersch to be so uniformly successful that it has come to be extensively employed in practical surgery for the purpose of covering large open wounds. Small flat pieces of skin are removed with the scissors or razor so as to include the epidermis, the rete Malpighii, and the upper layers of the corium, and then placed on the granulating surface and protected by suitable dressings.

The strips of skin are at first held fast by the coagulation of fibrin and nourished by transuded fluid; but soon embryonal vessels reach the transplanted part, and while the epidermal layers desquamate the deeper layers soon begin to form new epithelial cells and become the centers for a progressive new formation of permanent epithelium, which is provided with a horny layer by the metamorphosis of the cells upon the surface. Duhamel and John Hunter³ succeeded in transplanting spurs and teeth into the cock's comb, and Paul Bert made a rat's tail grow fast under the skin of its back.

From these and other experiments and observations it has been learned that young cells possess a greater power of proliferation than the old; that the transplanted cells must be abundantly nourished from the circulating blood; that the new-formed tissue soon undergoes atrophy if deprived of the stimulus of function; and that transplantation of tissue is successful only in animals of the same species.

Many animal cells remain alive for days after the general death of the organism. This power of independent existence has been called by Virchow

¹ *Die Specificität, Altruismus, und Anaplasie der Zellen*, 1893.

² *Virchow's Archiv*, lxx., 1877. ³ *The Natural History of the Human Teeth*, 1803.

the *vita propria* of cells. Periosteal cells have been found to retain their osteoplastic faculty for as long as one hundred and ninety-two hours after removal from the body (Morpurgo); and human cutaneous epithelium proliferated and produced living epithelial covering, when grafted on wounds, after having been kept outside of the body aseptically for from ten to twenty or more days (Ljunggren, Wentscher¹).

By some the tendency of cells to proliferate is regarded as connected with the nucleus. Under normal conditions the tendency is held in check, the stimulus to proliferate and the strength of the restraining influences being equally balanced. This equilibrium may be disturbed under pathologic conditions; on the one hand by factors that diminish or remove the restraining influences, and on the other hand by factors that stimulate the formative irritability of the cells, as Virchow states it. It is probable that the restraining influences are in part mechanic, due to the mutual pressure exerted by the cells composing a tissue, in part due to chemical conditions connected with the nutrition of the cells. These restraining influences become so relaxed and modified whenever destruction of cells occurs from any cause that the processes leading to cell division at once begin, and new cells are formed until equilibrium is again restored—*i. e.*, until as perfect regeneration as possible has been accomplished. That perfect regeneration often fails to take place depends upon such factors as insufficient power of proliferation, due to the age of the cells, their highly specialized state, insufficient or unsuitable nourishment, and upon the relatively greater regenerative faculty of less highly differentiated cells, as connective-tissue cells, the consequence being that very frequently the loss of substance is replaced largely by connective or scar tissue. At all events, regeneration may be ascribed, theoretically, as largely due to the removal or suspension by the wound or the cellular necrosis of the influences that in the structurally perfect tissue hold the tendency of the cells to multiply under control. That other factors than injury may lessen the restraining influences referred to cannot be denied, because cell proliferation also occurs under a number of conditions not associated with demonstrable trauma and necrosis.

The frequent occurrence of cell proliferation in tissues the seat of long-continued passive hyperemia has been ascribed to the increase of the nutritive supply, on the assumption that the nutrition of the cells is more of a passive process; but this view does not commend itself, because the nutrition of the cells is one of the manifestations of cellular activity, necessarily dependent, however, upon the presence of suitable food. It does not follow that an overnourished cell possesses an increased formative tendency. It is doubtful whether the infrequently renewed venous blood of passive congestion contains the elements capable of producing overnutrition. It is most probable that the proliferation in passive congestion is regenerative in character, and induced by the destruction of some of the more highly developed cells of the congested tissue.

It has been shown that a moderate degree of heat increases metabolism, and that the growth of the tissues in young animals is stimulated by a temperature of from 37° to 40° C.; whereas a temperature of from 10° to 12° C. delays growth and cell multiplication (Penzo).

There also seems to be no doubt that increased functional activity stimulates the nutritive as well as the formative action of the cells. The hyper-

¹ Ziegler's Beiträge, xxiv., 1899.

trophy and hyperplasia of increased labor (page 133) is best explained as due to a stimulation of the formative activity of the cell on account of the unusual demands made upon its functional capacity; that nutritive influences also play an important and sometimes decisive part in proliferation is shown, for instance, by the absence of hypertrophy of the heart under conditions that otherwise usually lead to its development, when there is a general malnutrition, as in chronic pulmonary tuberculosis or carcinoma of the stomach.

Whether traumatic, toxic, and infectious influences are capable of directly stimulating the cells to proliferation is a question that can hardly be answered definitely at the present time. In the majority of instances these agents produce either necrosis or necrobiosis of the cells with which they come in contact, and the proliferation that follows must be looked upon as regenerative in its nature, intended to fill the defect that has resulted. Often the proliferation extends beyond the requirements of regeneration. This question is of great importance in connection with the tissue proliferation that occurs in many chronic inflammations. The results of certain experiments seem to make it probable that chemical and bacterial agents may be able to incite cell proliferation directly. According to Baumgarten,¹ the first effect of the tubercle bacilli upon the rabbit's cornea is to excite cell division; Wegner² states that the administration of phosphorus directly increases the growth of bone; and Ziegler and Obolonsky³ found that small doses of arsenic and phosphorus seem directly to stimulate the cells of the liver and kidney to proliferation.

From these considerations⁴ concerning cell proliferation under pathologic conditions it may be concluded:

1. That the proliferation follows the physiologic types of cell division.
2. That the law of cell specificity is generally obeyed.
3. That proliferation is most active in young, well-nourished, only slightly differentiated cells.
4. That proliferation occurs under conditions that remove the restraint normally checking cell division, such as traumatism and necrosis; or that stimulate the formative activity of cells, such as increased function, heat, and certain chemical substances; or that operate in both ways at the same time.

REGENERATION.

Regeneration is the process by means of which portions of tissue lost are replaced by new tissue of the same, or approximately the same, structure as the original. It begins, as already indicated, with the formation of new cells by division of the pre-existing cells. These new cells are formative embryonal cells, which by further modifications and the secretion of an intercellular substance form the definitive permanent tissue.

Regeneration may take place not only after solutions of continuity due to external or violent means, such as wounds, but also after the destruction of cells such as occurs in the various forms of necrosis and degeneration that have been described. It depends, as stated above, upon certain peculiar qualities in the animal and human tissues that are not as yet understood,

¹ *Ueber Tuberkel u. ueber Tuberkulose*, 1885.

² *Virchow's Archiv*, iv., 1872.

³ *Ziegler's Beiträge*, iii., 1888.

⁴ An able discussion of some of the problems referred to is found in an address by Welch, on "Adaptation in Pathologic Processes," *Trans. Am. Phys. and Surg.*, iv., 1897.

but which are connected with changes in the environment or nutrition of the cells in the vicinity of a defect, in consequence of which the influences that hold in check the inherent tendencies of many cells to proliferate are overcome.

The power of regeneration in human tissues is limited as compared with that of many of the lower animals, in which whole organs and extremities may be produced. As a general rule, the higher the tissue stands in the scale of differentiation the smaller the tendency of its cells to proliferate. Thus, ganglion-cells are not reproduced to any extent, if at all, in the adult (the axis-cylinder, however, is easily regenerated), and many glandular epithelial cells have a relatively limited reproductive power; whereas the surface epithelium, the epithelial cells in the lining of ducts, and particularly the connective-tissue cells, have great power of regeneration. This unequal degree of regenerative faculty of the various histologic elements composing an organ or tissue is one of the factors that may lead to imperfect regeneration. In case the defect is not repaired by tissue of the same structure as the original, then substitution with connective tissue takes place. It is characteristic of connective tissue to fill all spaces not occupied by other cells, and this is also observed in the regeneration of pathologic defects. This imperfect, partial regeneration is designated as scar-formation.

The further study of regeneration necessitates a description of the regenerative processes as they present themselves in the individual tissues.

The Formation of New Blood-vessels.—New blood-vessels are formed whenever any considerable degree of hyperplasia or regeneration takes place. They are of the greatest importance, and, indeed, are often absolutely necessary in order that the proliferating tissue may receive sufficient nutrition. The formation of new vessels is therefore one of the very first as well as one of the most essential steps in nearly all forms of tissue proliferation.

Three kinds of vascular new formation have been described, namely, the primary, the secondary, and the tertiary.

The primary is the one observed in the embryo. The original view was that the cells of the mesoblast became hollow, the central part giving rise to red blood-corpuscles, while the remaining shells coalesced with each other to form the lumen and the wall of capillaries (Billroth).¹

In the secondary form spindle-shaped cells were believed to arrange themselves in rows so that an intercellular canal was formed, the lumen of which subsequently came into communication with the lumen of pre-existing capillaries.

The tertiary form was characterized by the development of budding processes in the walls of old capillaries, which united with similar processes, became hollow, and formed new capillary vessels (Billroth, Arnold²).

The secondary form is well demonstrated, although it is possible that in some newly formed tissues a certain degree of provisional circulation may make its way through intercellular canals and spaces without distinct walls. Regarding in the primary form Thoma³ and others claim that the development of the capillaries is not, as usually described, an intracellular, but an intercellular process, the mesoblastic cells arranging themselves in rows, the polygonal cells surrounding these spaces gradually changing into flat endo-

¹ *Die Entwicklung der Blutgefäße*, 1856. ² *Virchow's Archiv*, liii. and liv., 1871.

³ *Histogenese u. Histomechanik des Gefäßsystems*, 1893.

thelial cells. The primary form is not observed in the postembryonal period. The formation of vessels by budding (tertiary form) occurs in the embryo after the first network of capillaries is formed, and this is probably the only form of production of new vessels in postembryonal life.

The formation of new vessels by budding or sprouting presents in the main the following details: The protoplasm of an endothelial cell in a capillary wall becomes large and swollen, and sends out a solid, more or less wedge-shaped process or sprout, which ends in a long, fine, free thread.

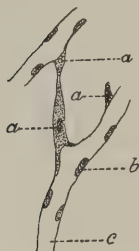


FIG. 40.—Formation of new capillaries by budding: *a*, budding process; *b*, nucleus of endothelial cell; *c*, capillary.

At about the same time the endothelial cells multiply by mitosis, and nuclei are seen in the protoplasmic bud. Subsequently the thread-like end unites with a similar prolongation from a neighboring sprout, or with the wall of either an adjacent capillary or of the capillary from which it sprang. Then this solid protoplasmic bridge becomes hollow; usually this occurs first at its point of origin, and blood at once enters the sprout, which gradually dilates and becomes pervious throughout to the point of entrance into another capillary; in this way a new passage for the blood is formed. The canalization sometimes begins from both ends of the protoplasmic bridge at the same time. New buds may spring from the original protoplasmic sprouts, quite a network of capillaries arising in a

very short time (Figs. 40 and 41).

The protoplasmic process from the endothelial cell must be regarded as a new cell after it has received its nucleus; and the formation of the new vessel is primarily an intracellular process, brought about by central canali-



FIG. 41.—New capillaries in a blood-clot on the inner surface of the dura mater. $\times 600$.

zation of the cells. As more nuclei develop in the homogeneous wall of the new vessel, new cells gradually appear, which are arranged so as to form a hollow cellular tube, in which the borders of the flat endothelial cells can be demonstrated by means of injections of silver-nitrate solution (Arnold). According to Ziegler, spindle-shaped or branching formative cells may unite

with the processes from the cells of the vessel-wall, become canalized, and thus aid in the forming of new capillaries.

The new capillary wall soon becomes thickened, either from proliferation of the endothelial cells or by the apposition of new formative cells from the surrounding tissue.

Every new formation of vessels begins with the production of capillaries. If new arteries and veins are formed, which always occurs in extensive tissue proliferation, then the lumen of the new capillaries undergoes dilatation and the wall increases in thickness. Whether this increase in thickness is due entirely to multiplication of the cells in the wall of the capillary or to apposition from without is not altogether clear; the method of new production of the muscular and elastic elements peculiar to arteries and veins is also not well understood.

Regeneration of Blood-corpuscles.—The regeneration of leukocytes takes place in the lymph-glands and lymph-follicles, the spleen, and the lymphoid bone-marrow. It has also been shown that the leukocytes may multiply in the circulating blood and in the tissue-spaces. The multiplication occurs both by mitotic and by amitotic division. The mitotic division gives rise to more durable and more vigorous cells than the amitotic division (nuclear fragmentation).

The regeneration of the red blood-corpuscles has been extensively studied, but unanimity of opinion concerning many details has not yet been reached. The studies of Neumann, Bizzozero, and others have established the presence of nucleated red blood-corpuscles—hematoblasts—in the bone-marrow of adults, and also that these cells divide by way of mitosis. It is generally agreed that in health regeneration of red blood-corpuscles occurs in the vessels of the bone-marrow, in which are found numerous nucleated red cells with karyokinetic figures. Inasmuch as the peripheral blood does not, as a rule, contain any nucleated red blood-corpuscles, it must be taken for granted that the regeneration occurs entirely in the bone-marrow, and that only the non-nucleated cells reach the general blood-stream. The transformation of nucleated into non-nucleated cells is due, according to most authors, to the vanishing (solution or extrusion) of the nucleus (Howell).¹

When generation of red blood-corpuscles goes on very actively, as, for instance, after an extensive hemorrhage or in chronic anemia, nucleated red cells may pass out from the marrow into the circulating blood.

It is in regard to the origin of the nucleated red cells of the bone-marrow that the opinions of investigators differ most. Bizzozero and Flemming hold that the nucleated red cells of the bone-marrow are direct descendants of the nucleated red cells of the blood of the embryo; these cells are collected in the blood-vessels of the marrow, and produce by mitotic division a continuous series of generations of nucleated cells, which change into the non-nucleated as occasion requires. Howell, Denys, and others believe, on the contrary, in the existence of colorless erythroblasts which change in the bone-marrow to hemoglobin-containing nucleated cells that afterward lose their nuclei and become the ordinary red corpuscles. These erythroblasts are formed, according to Löwit, in the bone-marrow and the lymph-glands.

Neumann finds Flemming and Bizzozero's conclusions inadequate. They do not explain the postembryonal formation of bone-marrow containing nucle-

¹ *Jour. of Morphology*, iv., 1890.

ated red corpuscles, as occurs when fatty marrow becomes lymphoid and when entirely new marrow is formed. He assumes, therefore, that nucleated red cells may develop from leukocytes or from the cells of the marrow.

Regeneration of Epithelium.—The view that connective-tissue cells play some part in epithelial hyperplasia and regeneration has been abandoned. The investigations of recent years have shown that epithelial cells originate only from epithelial cells; that the regeneration of epithelium occurs only from the multiplication of pre-existing epithelial cells; and, furthermore, that pathologic new growths of epithelial cells always spring from epithelium.

In all these instances the formation of new epithelial cells takes place by karyokinesis. Occasionally the body of an epithelial cell sends out processes which receive nuclei, separate from the maternal cell, and become independent cells.



FIG. 42.—Mitotic figures in regenerating corneal epithelium in a rabbit forty-eight hours after scratch with the point of a knife. Corrosive sublimate; paraffin; hematoxylin. $\times 1000$.

The epithelium covering the cutaneous and mucous surfaces is constantly undergoing desquamation, even under physiologic conditions, and the desquamated cells are replaced by mitotic multiplication of the remaining cells.

The regeneration of surface epithelium after loss of substance due either to traumatism or to necrosis and ulceration is usually perfect. In the intestine the surface epithelium, when lost, is replaced by proliferation of the cells in the follicles of Lieberkühn. The appendages of the skin, such as the hair and nails, are also reproduced, if parts of the hair-follicle and of the nail-matrix remain undestroyed. The epithelium of the cornea, which has been used extensively for the purpose of studying the histologic processes of regeneration, reproduces itself rapidly (Fig. 42).

It is possible that the epithelium of the sweat-glands and sebaceous glands may take part in the regeneration of the surface epithelium of the skin. Isolated islands of epithelial cells appearing in the center of granulating cutaneous surfaces, such as every surgeon has observed, spring in part at least from sweat-glands or sebaceous glands. In wounds of the trachea and the stomach it has also been shown that the epithelial cells of the gland-ducts take part in furnishing a new surface epithelium.

According to Fürst,¹ moderate degrees of heat and cold increase the capacity of the epithelial cells for regeneration.

Glandular epithelium is also capable of rapid regeneration. Thus, the liver possesses an extraordinary reproductive power; Ponfick² and Podwyssozki³ have found that the experimental removal of more than one-half of the organ is sooner or later fully replaced. Podwyssozki has also shown that after wounds of the liver cell-division by karyokinesis begins on the second day. In wounds and necrosis of the liver karyokinetic figures occur freely in the epithelial lining of the bile capillaries, as well as in the surrounding hepatic cells. The exact parts played by the epithelium of the biliary ducts and by the liver-cells proper in regeneration of the liver have not been accurately determined. In extensive wounds of the liver, as well

¹ Ziegler's *Beiträge*, xxiv., 1899.

² Virchow's *Archiv*, cxviii., 1889.

³ Ziegler's *Beiträge*, i., 1886.

as of other glands, the defect is closed by connective tissue, into which grow new-formed glandular structures to a greater or less extent.

The thyroid gland has been shown by Ribbert¹ to be capable of considerable local regeneration, even when it is the seat of goiter. The epithelium of the old follicles multiplies rapidly, and produces columns of cells that may arrange themselves so as to form new follicles.

The epithelium of the kidney is also capable of proliferation, and small losses in the tubular epithelium are rapidly replaced; but in wounds there is no restoration of the continuity of the tubules (Penzo, Barth). Extirpation of one kidney is followed by an adaptive or compensatory hypertrophy of the remaining organ, the beginning of which is indicated by the appearance of karyokinetic figures in the epithelium of the uriniferous tubules as early as the third day. Martinotti² has shown that while the old cells of the kidney excrete indigo-sulphate of sodium when injected into the blood, the new cells with karyokinetic figures do not take part in this process.

Cornil and Carnot have shown that the epithelium of the mucosa of the urinary bladder and the gall-bladder in the dog possesses a marked power of regeneration, especially that of the urinary bladder.

Ulcerative processes involving the mucosa and submucosa of the stomach and intestine, as well as defects produced by wounds, are followed by regenerative changes, in which new glands may be formed. The regeneration of the glands commences in the epithelium of the old glands, which proliferates and sends out new processes and tubules that spread over the base of the defect, filling the depressions and recesses. In this way even extensive ulcers may become clothed with a glandular mucous membrane; usually the arrangement of the glands in such cases is more or less atypical. In some cases the proliferation of the glandular tubules becomes excessive, and extends beyond the normal limits of the mucous membrane. This has been observed in the margin of healing gastric ulcers, and has been regarded as showing that the absence or diminution of the normal resistance to proliferation may act as a stimulus to the latter, and thus give rise to the growth of tumors (Ribbert).

As a general rule the various forms of epithelial cells are not interchangeable; flat epithelium produces flat, cylindric epithelium produces cylindric, etc. To this statement there are exceptions. In long-continued inflammations of various mucous membranes, accompanied by repeated desquamation of the epithelial lining, the continuously regenerating epithelium may change its form, so that a mucous surface covered with ciliated columnar epithelium becomes clothed with squamous cells. This has been observed to occur in the nose in ozena (Schuchardt); in the gall-bladder; in the uterus in the case of inversion, in uterine polypi projecting into the vagina, and in chronic endometritis (ichthyosis uteri, Ries³); in the middle ear in the case of polypoid formations that have penetrated the tympanic membrane and have reached the external canal. Under these circumstances superficial epidermization with flat cells may take place. In papilloma of the urinary bladder the stratified epithelium is replaced by cylindric cells.

The change of one form of epithelial cell into another is called epithelial metaplasia.

Regeneration in the Nervous System.—While peripheral nerves

¹ *Virchow's Archiv*, cxvii., 1889.

² *Centralb. f. allg. Path. u. path. Anat.*, iii., 1892.

³ *Am. Gynec. and Obstet. Jour.*, 1896.

are capable of complete regeneration, the central nervous system of man has no marked regenerative power. In animals the conditions vary; in many lower species and in newborn dogs and rabbits (Eichhorst and Naunyn¹) partial or complete regeneration has been observed after experimental injuries. In man wounds may be succeeded by the appearance of mitosis in adjacent ganglion-cells, but these do not appear to multiply (Sanarelli); after focal lesions, such as embolic and hemorrhagic softening, the defect is usually not filled in, even with scar-tissue, but a cavity is formed, the walls of which may show a zone of proliferating glia-tissue and a thickening of the perivascular connective tissue, but there is no regeneration of the nervous elements proper. Stroebe² has shown that in experimental wounds of the spinal cord the cut axis-cylinders, especially those of the pyramidal tracts, may grow out again to a certain degree, but not sufficiently to result in complete restoration, the defect being filled, as in man after similar injuries, with glia-tissue.

Regeneration of peripheral nerves presents many exceedingly interesting manifestations. It is in reality the regeneration of a part of a cell, inasmuch as the essential element concerned is the neuraxone, or axis-cylinder, which is part of the neurone.

Regeneration of the peripheral nerves has been extensively studied; while the interpretations of the microscopic appearances by the older authors differ greatly, recent investigators, such as Ranvier, Vanlair, Stroebe, Huber,³ and others, aided by an improved technic, have arrived at more uniform conclusions, although agreement has not yet been reached regarding all points.

When a peripheral nerve is cut, complete degeneration of the neuraxones and of the medullary sheaths distal to the wound follows, because those parts of the nerve have been severed from the centers of the neurones—the neurocytes. Central to the wound similar degeneration occurs in the cut ends up to the first or second Ranvier's node. This degeneration is characterized by disintegration of the medullary sheaths into drops and particles, while the neuraxones change into small fragments that soon disappear. Subsequently this detritus is gradually removed (Fig. 43). During this degeneration the nuclei of the sheaths of Schwann undergo mitotic division, and form protoplasmic cells which may coalesce into bands.

The division of a neuraxone is succeeded by certain obscure changes, such as chromatolysis, etc., in the corresponding neurocyte or ganglion-cell, which by some are interpreted as of a progressive and regenerative nature.

The regeneration of the nerve begins in the end of the central stump: the neuraxones swell up at the ends and split into from two to five new axones, which grow in a peripheral direction. Under the usual circumstances

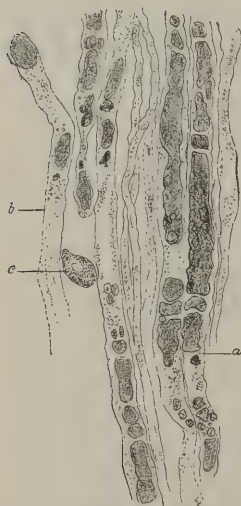


FIG. 43.—Degeneration in the sciatic nerve of a rabbit ten days after experimental division: *a*, neurilemma containing drops and fragments of myelin; *b*, empty neurilemma; *c*, leukocyte filled with detritus. Flemming's solution; paraffin; safranin. $\times 250$.

¹ *Arch. f. exper. Path.*, ii., 1874.

² *Ziegler's Beiträge*, xv., 1894.

³ *Jour. of Morphology*, xi. (with references).

the majority enter the peripheral part of the cut nerve and advance in its endoneurium and perineurium, or in the old neurilemma-sheaths (Fig. 44), until, after weeks or months, complete regeneration and functional restoration take place. Many axones may pass by the end of the peripheral stump and extend into the adjacent tissue. Perfect apposition of the cut ends and the interposition of as little as possible of the granulation-tissue which always forms in the wound favor the growth of the new neuraxones within the old nerve; a dense cicatrix between the ends may prevent the down-growth of the fibers. According to Vanlair, regenerating nerves may grow from 0.2 mm. to 1 mm. a day, according as the tissue they penetrate is favorable or not. In the completely regenerated nerve the rearrangement of the new fibers into bundles takes place a certain distance below the wound.

The new axones gradually receive medullary sheaths, which at first have a varicose appearance; the origin of the myelin has been traced to the cells

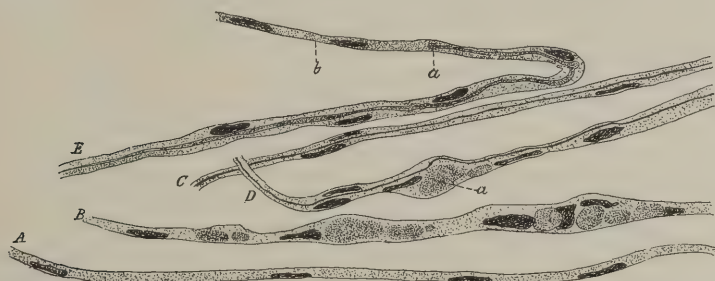


FIG. 44.—Teased specimen of divided nerve one hundred and seventeen days after section (after Huber). *A*, completely degenerated fiber; no regeneration. *B*, degenerated fiber containing balls of broken-up myelin. *C* and *D*, new fibers with axis-cylinders and nerve-corpuscles; at *a*, fragment of myelin. *E*, fiber with axis-cylinder ending in slight enlargement at *a*; *b*, continuation of old sheath containing protoplasm and nerve-corpuscles. Stroebe's stain. $\times 700$.

of the sheath of Schwann, but it is more likely that the new myelin covering is the result of a continuous down-growth of the old.¹ In fact, the claims that the new axones and myelin sheaths result from the union of pieces produced by the cells of Schwann's sheath are not in harmony with our present conception of the neurones. The cells of Schwann's sheath are connective-tissue cells, and their function in regeneration of nerves seems to be phagocytic, rather than the formation of parts of the neurones proper.

Huber has shown that after loss of substance in peripheral nerves regeneration and restoration of function are materially favored by implanting between the resected nerves a loose segment of a nerve. The implanted segment and the peripheral stump, together with about 0.75 cm. of the central stump, degenerate, and both the implanted segment and the degenerated nerves soon present the same structure, namely, collapsed sheaths containing nucleated protoplasmic bands; the new axones grow into and between the sheaths of Schwann. The implanted piece of nerve serves as a path along which the new axis-cylinders can grow into the old nerve. Various other substances, such as catgut, bone tubes, etc., have been used for the same purpose, but not with such satisfactory results.

When the central end of a completely severed nerve is placed outside of

¹ Kölster, *Ziegler's Beiträge*, xxvi., 1899.

communication with the peripheral part, as occurs in amputations and very extensive wounds, a mass of embryonal connective tissue forms around the end of the nerve. Axones may sprout from the end of the nerve-stump and grow into the cicatricial tissue in all directions, forming a distinct bulbous enlargement of the nerve-end. This is the so-called amputation neuroma. It represents an effort at regeneration of the axones.

Regeneration of Muscular Tissue.—Striated muscular tissue is capable of a certain degree of regeneration. New muscular tissue is formed only from the old, and not from connective tissue, which may, however, take part in the formation of the sarcolemma of the new fibers. The regeneration of striated muscular tissue can take place independently of any nerve-supply. It has been studied as it occurs after experimental wounds and after necrosis in typhoid fever (Waldeyer, Neumann, Nauwerck, Volkmann,¹ and others).

Regeneration of muscular tissue begins with the mitotic division of the nuclei of the contents of the sarcolemma. The new nuclei lie upon as well as in the spaces between the split ends of muscular fibers. There is soon noticed the formation of new protoplasm around the nuclei, and large multinucleated protoplasmic masses form, into which the existing striated muscular substance passes without sharp limits. The new muscular fibers develop from these multinucleated protoplasmic masses, increasing in size and length, and gradually presenting first a longitudinal and then a transverse striation. The new muscular fibers frequently split up into two or three narrower fibers, so that more fibers result than originally were present.

The dividing muscle-cells that are not in connection with living sarco-plasm also change into multinucleated protoplasmic masses, which often contain hyaline substance and fragments of old fibers. Such masses are usually found in great numbers in the early scar after wounds or necrosis of muscle. While the larger part of these cells probably disintegrate, it is likely that some of them change into striated muscle-substance, and form either new muscle-fibers or become united with old muscle-fibers or with new buds. This is the regeneration in discontinuity of Volkmann, and occurs especially after necrosis of muscle in typhoid fever.

Reproduction of the muscular tissue of the heart occurs to an extremely limited degree. Wounds and necroses heal by means of scar-tissue.² Hypertrophy of the heart is chiefly a true hypertrophy, although it is probable that some hyperplasia takes place.

The reproduction of smooth muscle-fibers occurs to a certain extent after traumatic and other necroses, as well as in hypertrophy and in tumors. The regeneration occurs by mitotic cell division. Whether transformation of embryonal connective-tissue cells into smooth muscle-fibers occurs, as was thought by Kölliker, and whether there is ever metaplasia of smooth muscle-fibers into striated, as maintained by Busse, is still undecided. The power of regeneration of smooth muscle seems to be limited, as wounds in the muscular coat of the stomach, the intestine, and the urinary bladder are largely closed by scar-tissue.

Regeneration and Metaplasia of the Connective Tissues.—

The connective tissues—ordinary connective or fibrous tissue, periosteum, bone, cartilage, myxomatous and fatty tissue—are all made up of embryologically equivalent mesoblastic cells, the marked variations in the structure

¹ Ziegler's *Beiträge*, xii., 1893 (with references).

² Elsberg, *Jour. Exper. Med.*, iv., 479, 1899.

of the mature tissues depending essentially upon the differences in the intercellular substance.

The regeneration of these tissues begins with the production of an indifferent embryonal or formative tissue, from which the definitive tissue is produced by the development of peculiar intercellular substance. The connective tissues are also able to change the one to the other without the intervention of an embryonal stage by a change of the intercellular substances only, a process called metaplasia. Thus, cartilage may change into bone, and fibrous connective tissue into cartilage, etc., by a transformation of the matrix in each case.

The mature connective tissues possess different degrees of regenerative power. It is most marked in the ordinary fibrous connective tissue, in periosteum, and in the medullary tissue of bone; whereas cartilage and bone-substance proper possess but little ability to form new tissue, so that in them larger defects are repaired either by proliferation of periosteum (perichondrium) or of ordinary connective tissue with subsequent differentiation of the matrix, or the defects are filled with scar-tissue.

The question of the development of connective tissue from hematogenous cells is touched upon in the discussion of inflammatory granulation-tissue. The theory of Shakespeare, and more particularly of Grawitz, that the intercellular substances of many tissues, as the tendon, for instance, contain invisible slumbering cells that are roused into active proliferation by the influence of regenerative and other stimuli, is not supported by any facts that would warrant its discussion at the present time.

Regeneration of connective tissue begins with mitotic division of pre-existing cells. If defects of any extent are to be repaired, the proliferation continues actively until a mass of young cells is produced—embryonal, formative, or granulation-tissue. Simultaneously new capillaries are formed by budding processes from the old. It is quite likely that the capillary endothelial cells also give rise to formative cells, as already described. The embryonal cells are larger than the small mature cells of the connective tissues; the form of the cells varies, depending upon conditions of pressure and upon the age of the cells; round, oval, spindle-shaped, and branching cells are observed; the nuclei are large, often vesicular, and there may be large cells with two or many nuclei—giant cells. These formative cells have received various names, depending upon the kind of mature tissue they are destined to form in the process of further differentiation—if fibrous tissue, fibroblasts; if cartilage, chondroblasts; and if bone, osteoblasts.

Fibrous Tissue.—When fibrous tissue is reproduced, as in the healing of wounds and defects in the organs and tissues of the body, there is formed an intercellular substance, or matrix, in part homogeneous, in part fibrillated. Concerning the manner of formation of the intercellular substance, investigators express different opinions. Some claim that the fibroblasts produce a homogeneous intercellular substance which subsequently becomes more or less finely fibrillated; others, that the protoplasm of the cells first forms fibrillæ in its peripheral layers, which are subsequently deposited between the cells; the direction in which these fibrillæ run is determined by the mechanic tension of the tissue.

The manner in which new elastic tissue is formed is not definitely known. The new formation of elastic elements has been studied lately, especially in various forms of endarteritis. Some investigators hold that they are formed

by chemical changes in the stroma, others by such changes in the protoplasm of connective-tissue cells.¹ As the intercellular substance is formed the fibroblasts become smaller and flattened, and lie as fibrous connective-tissue corpuscles in small spaces in the matrix. When a wound or defect becomes filled up with a finely fibrillated connective tissue produced in this manner, a scar or cicatrix is said to have formed.

Cartilage.—Formative tissue composed of chondroblasts may be produced to a limited extent by existing cartilage-cells, but originates generally from mitotic division of cells in the periosteum or perichondrium, the medulla of bone, and sometimes in connective tissue. The chondroblasts produce a hyaline intercellular substance which gradually increases in amount, while the cells become smaller and lie as cartilage-cells in small round cavities, about which the matrix becomes more dense, so as to form a sort of capsule for the cells (Fig. 45). New cartilage is also frequently produced by metaplasia. This occurs, for example, in the perichondrium of growing cartilage by a gradual change of its fibrillated intercellular substance into the homogeneous hyaline material of cartilage, while the connective-tissue cells assume the form of cartilage-cells. Hyaline cartilage may change into fibrocartilage by the formation of fibrillæ in the matrix. Cartilage may by metaplasia change into the other connective tissues.

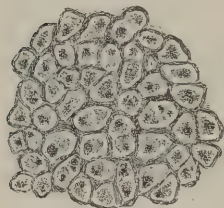


FIG. 45.—New-formed cartilage about a seven-day-old fracture of the tibia in a rabbit. Flemming's fixation; saf-ranin. $\times 450$.

Bone.—The formative tissue arises principally from the cells of the periosteum, the perichondrium, and the bone-marrow; but it may be produced by fibrous connective tissue. The osteoblasts become separated by a homogeneous or densely fibrillated ground substance, which subsequently becomes impregnated with lime salts; while the osteoblasts change into small irregular cells, which come to lie in small cavities as the bone-cells of mature bone. Before calcification takes place the ground substance is known as osteoid tissue. The formative tissue between the areas of osteoid tissue changes into the structure of bone-marrow; the cells send out processes which unite with those from other cells at the same time as a sparsely fibrillated, fluid, intercellular substance is formed, and in this substance the cells characteristic of bone-marrow are subsequently deposited. When the osteoid tissue has become infiltrated with lime salts the osseous structure is completed.

Usually, however, this process of bone formation is associated with metaplastic changes. Thus, the formative tissue may first produce hyaline cartilage, which subsequently becomes vascularized, and then by metaplasia changes into osteoid tissue, which becomes impregnated with lime salts, while the cartilage-cells become bone-cells. Osteoid tissue is distinguished from osseous tissue by the absence of lime salts, and from cartilage by the irregular outline of the cells and the greater density of the intercellular substance. These various processes are described more completely in connection with the healing of fractures. Connective tissue as well as pre-existing cartilage may also change into bone directly, according to the principles of metaplasia.

Fat Tissue.—New fat tissue may arise by the deposition of fat in the

¹ Jores, "Neubildung elastischer Fasern in der Intima bei Endarteritis," *Ziegler's Beiträge*, xxiv., 1898.

cells of formative tissue, or in myxomatous or fibrous connective tissue. When myxomatous tissue changes into fat tissue the star-shaped cells become globular fat-cells, while the intercellular mucoid material vanishes. The medullary tissue of bone may become changed into fat tissue—fatty marrow—in the same manner.

Myxomatous Tissue.—Myxomatous tissue may be produced from formative tissue by the appearance of a homogeneous, jelly-like intercellular substance which contains mucin, while the cells send out processes that form a network. It may also arise by metaplasia from any of the other connective tissues. When fibrous tissue changes into mucoid tissue the fibrillated intercellular substance disappears, and in its place appears mucoid material, while the connective-tissue corpuscles change into cells with interlacing processes. In an analogous manner cartilage, bone, and fat tissue may become transformed into myxomatous tissue.

Lymphadenoid Tissue.—Lymph-nodes are the seat of a constant physiologic regeneration of lymphocytes. After loss of substance or in pathologic new formations the endothelial cells and the cells of the connective-tissue framework proliferate; new reticulum is formed, in which lymphocytes and large endothelial cells accumulate.

HYPERTROPHY.

Hypertrophy is the increase in the size of an organ or tissue due to an increase in the size or in the number of its cells, or to both, without any appreciable alteration in its structure. As a general rule, hypertrophy depends upon an increase in the number as well as in the size of the cells of an organ or tissue. When it is due entirely to an increase in the size of the cells it is often denominated *true hypertrophy*; and when it is due to an increase in the number of the cells it may be designated as *numerical hypertrophy*, or *hyperplasia*. The existence of true hypertrophy can only be determined by painstaking micrometric measurements of the individual cells of the organ in question. As indicated, hypertrophy is accompanied by an increase in the size of the organ affected; in hollow organs, as the heart and urinary bladder, the increase in tissue may take place at the expense of the cavity enclosed (concentric hypertrophy). The most exact idea of the degree of hypertrophy present in an organ is obtained by comparing the weight of the organ with the normal standard. It is to be remembered that increase in size as well as in weight may depend upon many other causes besides hypertrophy, and consequently it is important to be sure that an apparently hypertrophic tissue possesses a normal structure.

Hypertrophies not dependent upon a congenital tendency to excessive growth usually result from an increase in the functional demands placed upon the organs and tissues. Such hypertrophies are therefore very properly spoken of as *labor* or *functional hypertrophies*; they are observed particularly in muscular and glandular organs. The physical and chemical changes in the muscle-cell or gland-cell incident to increased function in some way lead to cell growth (Welch). In certain diseases of the arteries—arteriosclerosis—there is a marked increase in the resistance to the blood-current, to overcome which the heart must increase the strength of its contractions; in stenosis of the valvular orifices, or in insufficiency of the valves of the heart, disturbances result in the mechanic apparatus of the organ that mate-

rially increase the labor necessary to maintain the circulatory equilibrium ; in these and similar instances the heart-muscle usually undergoes hypertrophy, and thus in a measure it fulfils the extra requirements placed upon it. By so doing, it compensates for the disturbances of the circulation produced by the vascular and valvular disease, and hence the hypertrophy is generally called compensatory hypertrophy.

Compensatory hypertrophy of the heart usually develops when there is necessity for it, provided the general condition of the nutrition is favorable ; it develops more readily in young than in old persons—facts illustrating the influence of functional increase, nutritive supply, and of age upon the growth and proliferation of cells.

Similar hypertrophy may develop under analogous conditions in the arteries, the uterus, the urinary bladder, the ureters, the stomach, the intestines, and the skeletal muscles. The uterus during pregnancy is the seat of an enormous hypertrophy, the increase in the size of the muscle-fibers being many times that of those of the nonpregnant organ. Moderate increase in the obstruction to the outflow of urine will be overcome by a compensatory hypertrophy of the bladder ; in narrowing of the pyloric orifice and in gradual intestinal obstruction the stomach and the intestines often become greatly hypertrophied. A persistent increase in the tension of the arteries has been shown by Thoma to lead to an increase in the thickness of the media.

Examples of compensatory hypertrophy are also frequently observed in connection with glands. Thus, if one kidney is destroyed, congenitally absent, or rudimentary, then the remaining kidney performs the function of both, and soon presents a greater or less degree of hypertrophy. In the case of congenital absence or marked hypoplasia of one kidney the remaining organ may increase to such an extent as to weigh as much as both kidneys together ordinarily do ; but if the loss of one kidney occurs after the growth of the body has been completed, then the hypertrophy of the remaining kidney is much less marked—another example of the greater power of hyperplasia of youthful tissue than of old. In the case of the kidney the compensatory hypertrophy has been shown by a number of studies (Grawitz and Israel, Nothnagel, and others) to depend in part upon a true hypertrophy, in part upon a hyperplasia of the glomeruli and uriniferous tubules.

When the liver sustains an extensive loss of substance, then the remaining portion undergoes hypertrophy. After extirpation of one adrenal there ensues hypertrophy of the other (Stilling). Compensatory hypertrophy of the testicles, ovaries, and mammary glands may occur (von Recklinghausen, Ribbert). After removal of the whole or part of the thyroid hypertrophy occurs in the remaining portion and in such accessory thyroid glands as may possibly be present, and in all probability also in the hypophysis (Rogowitsch, Stieda)—a fact pointing to a functional relationship between the thyroid and the hypophysis.

Among other instances of compensatory or adaptive hypertrophy may be mentioned the great enlargement of the normal lung when its fellow has failed to develop (agenesia), and the extensive hypertrophy of the fibula when the tibia is rendered useless in the support of the body (Sutton).

Hypertrophy (hyperplasia) of the lymph-glands, the lymphadenoid tissue in general, and of the spleen (leukemia), and also of the thyroid gland (goiter), occurs under conditions for which we have as yet no very definite explanation.

Tissues subject to constant wear may become greatly increased in size when, for any reason, the continual loss of substance ceases. Overgrowth from lessened waste occurs especially in connection with the dermal organs, such as the nails, hair, and teeth. If the wear of the nails be prevented, as in bedridden patients, they are sure to attain considerable proportions (hyperonychia, onychogryposis) (Fig. 46). Similar overgrowths are observed in the horny portions of the feet of animals, the beaks of birds, and the teeth of rodents. According to Sutton, the growth of the incisor teeth of rodents is unconditional, unless held in check by constant usage. They may grow to excessive length under any of the following conditions: 1. Slight mobility of the tooth in its socket. 2. Diminished usage, as when rodents are in captivity. 3. Loss of antagonism of the teeth, either from fracture of a tooth or injury to the maxillæ, leading to displacement of the parts (Fig. 47). The great overgrowth that follows may lead to perforation of the skull. The tendency of these teeth to grow in a circle is explained



FIG. 46.—Overgrowth of the nail of the big toe in a bedridden person.



FIG. 47.—Overgrowth of the incisor teeth of a woodchuck, due to loss of apposition on account of fracture of the lower jaw.

as due to the fact that in gnawing the posterior part of the teeth yields first, the anterior hard coating of enamel being the last to yield (Sutton).

Among overgrowths of congenital nature are the so-called giant growth, in which the body reaches an excessive size, and partial giant growth, in which one extremity, one finger, or some other portion of the body presents a relative excess in bulk. Similar overgrowths may occur in special tissues, as the skin or its appendages (ichthyosis, hypertrichosis), in bones (acromegaly), etc. Overgrowths of this kind must be ascribed to conditions depending either upon an excessive number of cells, upon the presence of cells with an exaggerated tendency to multiply, or upon the absence of the influences that ordinarily restrain the growth of tissues.

INFLAMMATION.

THE STUDY OF THE REACTIONS OF THE ORGANISM TO INJURY.

Introduction.—The exact significance of the word inflammation cannot be compressed into the narrow frame of a dogmatic definition. The views held of the limitations of the term inflammation vary. As will be seen from a perusal of the descriptions in this book, inflammation is a complex local process composed of disturbances of the circulation, of retrogressive and progressive changes, associated in varying degrees, and initiated by a variety of injuries. The general consideration of the nature of these processes at

one time, under the heading of inflammation, is warranted by reason of their common mode of origin. The external, obvious manifestations of the process may vary according to the kind of tissue and the intensity of the changes; but close examination shows that in each case virtually the same succession of changes follows the action of different causes. The comparative study of the action of injuries throughout the animal kingdom has shown that the same general principles underlie the resulting phenomena in the cells and tissues. Hence it will suffice for the present to regard the inflammatory changes as the local reaction of the tissues to injuries and lesions of various kinds. Herein is implied that some, at least, of the changes diminish the effects of the injury; that the reaction is salutary.¹

EXPERIMENTAL INFLAMMATION—THE STUDY OF THE REACTION TO INJURIES IN ANIMALS.

Metschnikoff² and others have shown that unicellular organisms rid themselves of foreign particles either by solution, through the action of digestive vacuoles containing an acid ferment, or by extrusion; and that losses of substance are readily repaired provided the nucleus persists.

In multinuclear organisms the reaction becomes more and more complex. In the echinoderms Metschnikoff found that when the epiblast is punctured by a foreign body, wandering mesodermal cells move toward the foreign body, attach themselves to it, and fuse into plasmodial masses, the function of which seems to be to isolate and remove foreign substances. Smaller bodies, such as living bacteria, are digested by single mesodermal cells, which ingest the bacteria by sending out pseudopods. Such cells are also known as *phagocytes*. This reaction is in no way influenced by the nervous or vascular system. The remarkable power of repair in the lower *Metazoa* is well seen in the *Hydra*, which may be divided into several pieces, from each of which a new individual is formed.

Among the *Metazoa* with an incomplete vascular system it has been shown that leukocytes move actively toward regions of injury or infection, and surround foreign bodies that are present; many of the leukocytes act as phagocytes, incorporate and digest small particles; others are not phagocytes, but contain granules that stain with acid dyes, and that are readily extruded; of the fixed cells, the endothelial cells especially may act as phagocytes.

In the higher animals the simplest conditions after injury are furnished by the avascular tissues, such as the tail-fin of the young axolotl and newt, or the cornea in higher forms. By depositing with a needle a few grains of carmin in the tail-fin of the axolotl a certain number of cells are destroyed, and the living cells in the immediate vicinity become swollen and vacuolated; wandering cells in the spaces between the fixed cells move toward the area and take up the grains of carmin and the cellular detritus, while the epidermis folds over and covers the wound; this is followed by regeneration of the lost cells and the return of the tissue to its normal state. In this course of events the vessels need not take any part whatsoever.

The course of inflammation in the cornea has been studied repeatedly, and

¹ For full references to recent literature on inflammation, consult J. George Adami's article in Allbutt's *System of Medicine*, i., 1896.

² *Pathologie comparée de l'Inflammation*, 1892.

with the most diverse results ; but the correctness of the following statements cannot be questioned. The cornea is perfectly avascular ; it is composed of fibers ; between them is a network of spaces, bathed with lymph, in which lie the corneal cells. When a small area of the anterior surface is destroyed by means of zinc chlorid or other caustic agent, a small opacity soon forms, due to the accumulation of leukocytes about the injury. The leukocytes move actively into the area from the lymph-spaces in the cornea itself and from the lacrimal fluid bathing the conjunctiva. The next step consists in the regeneration of the cells originally destroyed. When a small quantity of a bouillon suspension of the *Staphylococcus pyogenes aureus* is brought into the cornea with a needle, a few of the corneal cells about the cocci are killed ; as the cocci multiply the necrosis extends, and at the same time leukocytes are attracted toward the area and fill the lymph-spaces in its vicinity. In such experiments the reaction may extend to the vessels at the corneal margin, which become dilated and congested, the leukocytes passing through the vessel-walls and toward the micro-organisms. The leukocytes take up some of the cocci into their interior, where the cocci may perish ; but it is equally possible that the leukocytes may die in consequence of the action of the cocci, and, if the latter are relatively virulent, extensive necrosis and loss of corneal substance may ensue—an ulcer forms. Sooner or later as the cocci die the extension ceases. In the mean time leukocytes accumulate more and more in the corneal spaces ; vascular sprouts grow into the cornea from the margin ; and finally processes of proliferation of the corneal cells and definitive repair begin (Councilman).¹

In vascular tissues the inflammatory reaction reaches the highest degree of complexity, but gradations in the process from the mild to the more intense are observed. Uncomplicated aseptic incisions heal with a minimum of reaction. Some reddening of the margins of the wound, due to congestion of the vessels, and the formation of a thin fibrinous layer on its surface, usually take place, and a few leukocytes wander out into the margins of the injured spot ; but the main role is played by the fixed cells, which enlarge and send out processes that may interlace, at the same time as new cells are formed to replace those destroyed ; new capillaries are also formed. The changes here are essentially regenerative.

A general survey of the events in acute inflammation of a vascular tissue is best obtained by studying the changes that occur in such transparent parts as the tongue, the mesentery, and the web of the frog, and the mesentery of rabbits and other warm-blooded animals, after injury. Such experiments were first made by Cohnheim in 1867. It has been found that the acute inflammatory changes are the same in virtually all vascular tissues, including those of man. In some of the tissues experimented with, it is necessary to apply a chemical irritant or to produce a slight loss of substance in order to induce reactive changes ; in others, as, for instance, the mesentery of the frog, mere exposure to the air is sufficient. A curarized frog is taken, and an incision is made in the left flank, through which a loop of small intestine is carefully drawn out, and fastened by means of pins to strips of cork glued to a glass slide, or it is merely stretched over a glass cube fastened to a glass plate in such a manner that a portion of the mesentery is conveniently arranged for microscopic examination ; or the web of a

¹ The character of the exudation in acute keratitis of the rabbit, *Tr. Chicago Path. Soc.*, 1900, iii., 68-85.

small frog may be taken, a small piece of the skin nipped off, and the subsequent changes studied under the microscope.

In such experiments it will be seen that the blood circulates through the vessels in two distinct currents, namely, the central, or axial, containing the red and white blood-corpuscles, and the marginal, peripheral, or plasmatic current, which ordinarily is free from corpuscles. Very soon after the exposure of the mesentery dilatation of the arteries with increased rapidity of the current follows—an active hyperemia—and dilatation of the veins and capillaries gradually ensues, and the current becomes slowed. As the current becomes slower the leukocytes accumulate in the plasmatic zone in the veins, while in the capillaries the red and white corpuscles are mixed irregularly. The circulation in the capillaries becomes disturbed; now it stops, then it moves on again, only to stop for a little longer time; the number of leukocytes in the capillaries also seems to increase in proportion to the red cells. The distinction between the marginal and the central zones in the veins is soon lost, and the corpuscles gather near the walls of the veins. Individual leukocytes apply themselves very closely to the inner surface of the vessels; soon a small projection appears on the outside of the capillary or vein; while this projection grows larger the intravascular part of the cell grows smaller, until the whole leukocyte lies outside of the vessel, and perhaps moves away from it by means of active ameboid movements. The leukocytic emigration may be very marked. In the meantime the dilatation of the vessels and the slowness of the current may have become extreme, so that in some vessels there is almost complete stasis. Red corpuscles may have been pressed out into the tissue either by diapedesis or rhexis. At the same time it is evident that considerable plasma has exuded into the tissues, and, becoming mixed with broken-down leukocytes, it may give rise to the precipitation of fibrin, whereby the field becomes more and more obscure, as if covered with a fibrinous deposit.

Such observations as the above may have to be prolonged for hours in order that all the details outlined here may be studied.

The subsequent events it is practically impossible to follow by continuous observation under the microscope. Suffice it to say that the leukocytes may disintegrate or wander away, that the vessels may return to their normal caliber and the current be re-established, while rapid cell proliferation points to active repair; or micro-organisms may enter the tissues and cause extension of the process. The microscopic examination of properly fixed and prepared tissues that during life were the seat of inflammation is the principal method of study of the successive stages of the retrogressive and progressive changes in the farther stages of the process; and it has been learned that the proportion of the various constituents of the blood in the exudate, as well as the nature of the changes in the fixed tissues, varies greatly in different instances of inflammation.

These brief considerations will serve to emphasize that the same general principles underlie in all animals the reactions to injuries. In the lower animals wandering cells play the principal part in ridding the organism of injurious substances. In the higher animals the accumulation of leukocytes and wandering cells in the injured area is a constant and perhaps the most striking feature of the inflammatory reaction. In vascular and, to a certain extent, about avascular tissues important changes in the blood-vessels occur that lead to exudation and favor leukocytic emigration. Later phases of

the process, namely, proliferation of fixed cells and repair, are closely connected with the early reactive changes, and both sets of phenomena may be regarded as stages of a single process.

THE FACTORS IN THE INFLAMMATORY PROCESS.

On account of the intricate structure of the principal tissues in the higher animals a number of distinct factors take part in the inflammatory process. The parts taken by the vessels, the nervous system, the leukocytes, the exudation, and the fixed cells all demand consideration.

The Vessels in Inflammation.—Cohnheim regarded the changes in the vessel-walls as of fundamental and primary importance in inflammation. The exact nature of the changes could not be explained, but alterations took place that resulted in increased porosity or permeability, allowing plasma and corpuscles to pass through. The study of the role of the leukocytes in inflammation, of the action of the serum, of the adaptive tendency of the whole process, has profoundly modified this early conception.

Nevertheless, distinct alterations of the structure of the walls of the vessels are thought to occur in inflammation, principally because the composition of the exudate corresponds closely with that of the blood-plasma, thus pointing directly to an increased permeability. Such alterations are not always morphologically demonstrable; they may exist in the cement substance between the cells, where changes are usually seen after inflammation, the traces left by the migrating leukocytes being quite distinct in silvered preparations. Whether the alterations in the vessel-walls are altogether passive and due to the lesion produced by the harmful agent, such as pathogenic micro-organisms, or whether they are active and purposive, due to contractions of the endothelial cells which open the pores between them, so as to allow the passage of blood-cells and blood-plasma, cannot be stated precisely. In severe inflammatory lesions the walls of the blood-vessels may suffer retrogressive and passive changes that increase the porosity and lead to circulatory disturbances; they may be torn on account of the violence of the hyperemia or by the necrotic action of toxic substances on the cells. Stricker, Klebs, and others have found that the endothelial cells are contractile and may change their position: this property must play an important part in the formation of stomas in inflammation. It is therefore not improbable that some of the alterations in the vessel-walls are active processes which facilitate the leukocytic migration and serous exudation. Leukocytes are, however, fully able to traverse normal walls.

The endothelial cells are not only contractile, but also, according to Metschnikoff, phagocytic and mobile. This is true also of the lymphatic endothelial cells and of the cells lining serous membranes. Thus, tubercle bacilli, malarial organisms, and various other microbes, as well as different substances, such as pigments, are frequently taken up by endothelial cells, especially those of the liver. Inasmuch as some of the micro-organisms are immobile, their presence within the protoplasm of endothelial cells must be attributed to an active cellular process.

In agreement with these functions, the endothelial cells in inflammation frequently enlarge and project into the lumen of the vessel, causing an increased resistance to the blood that tends to slow its rate of flow; the nuclei of the cells also stain more deeply, and mitosis may occur; in many

acute and chronic inflammations intravascular and other proliferation often takes place, and is usually traceable to the endothelium. Moreover, in regenerative and other proliferations the endothelial cells, by budding, give rise to new capillaries.

Whether the secretive function claimed by Haidenhain for normal endothelial cells influences the composition of the exudate in any way has not been determined. By the addition of substances derived from disintegrating cells the composition of the exudate becomes greatly altered after it leaves the vessels.

The Influence of the Nervous System in Inflammation.—

In former times vasomotor disturbances, either in the sense of paralysis (Henle) or of spasm (Brücke), were regarded as the essential causes of the whole process of inflammation. Cohnheim demonstrated, by cutting all the tissues connecting the tongue of a frog with the body, with the exception of the artery and the vein, that acute inflammation proceeded in a fairly typical manner without the intervention of central nervous influences.

Ordinarily the nervous system exercises a direct influence on the inflammatory process. Samuel showed that if the sympathetic (vasoconstrictor) is divided on one side, and the auricular branches (vasodilator) on the other side, there is a marked difference in the inflammatory reaction in the ears of the rabbit when they are placed in water warmed to 54° C. The ear the sympathetic of which has been cut manifests an acute inflammation proceeding rapidly to recovery; whereas the ear deprived of the vasodilator influence becomes the seat of stasis without hyperemia, and necrosis finally ensues. Similar results were obtained by Roger after injecting cultures of the streptococcus of erysipelas into ears under the same conditions. In the ear the auricular nerves of which had been cut the erysipelatous inflammation lasted long and mutilation resulted; on the side with the sympathetic divided the inflammation ran a more rapid course to recovery. These experiments indicate clearly the influence of nerves on inflammation. The uncontrolled action of the vasoconstrictors interferes with hyperemia and exudation; the noxious substances are not removed; repair is delayed. Under the action of the vasodilators the stages are hastened and rapid recovery follows.

The powerful influence of the nervous system is also shown by the fact that hypnotic suggestion may be followed by at least some of the local symptoms of acute inflammation.

The Leukocytes in Inflammation.—The Leukocytic Emigration.

—One of the most striking features in inflammation is the peripheral disposition and the emigration of the leukocytes. The emigration of leukocytes was first observed by Dutrochet in 1828. Gulliver in 1842 compared the cells in pus to leukocytes. Addison in 1843, and Waller again in 1846, demonstrated the emigration of leukocytes, but these observations were forgotten until Cohnheim discovered the process anew in 1867.

As already observed, the blood-corpuscles are normally carried along in the axial current of the circulating blood, while the marginal zone is almost wholly plasmatic. The red corpuscles are found in the center and the white cells in the peripheral parts of the axial stream. The cause of this arrangement of the cells in the current has been shown by Schklarewsky and D. J. Hamilton to depend upon the relative specific gravity. When small bodies of different specific gravity are made to circulate in fluids through a series

of tubes, it is found that the heavier bodies run in the center of the stream, and the lighter bodies—in the case of the blood, the leukocytes—tend to gather in the marginal zone. When the current becomes slow the heavier bodies—the red cells—also pass into the periphery of the stream, and the axial character of the current is lost. While the slowing of the current in inflammation undoubtedly favors the peripheral arrangement of the cells, it does not fully explain the characteristic margination or “peripheral drift” of the leukocytes, which does not occur in merely delayed flow. As the leukocytes in inflammation reach the peripheral zone of the plasma-stream they move backward and forward for a little time (Landowsky); but soon they attach themselves to the wall, spread themselves out in close contact with it, and finally passage through the wall—emigration—follows (Figs. 48 and 49).

Arnold and others have shown by silvering the outlines of the endothelial cells that the emigration occurs through the cement that holds the cells together; after emigration the silver lines are broader, and present circumscribed pores that are regarded as traces left by the migrating cells. According to Löwit, emigration may even occur without any changes in the

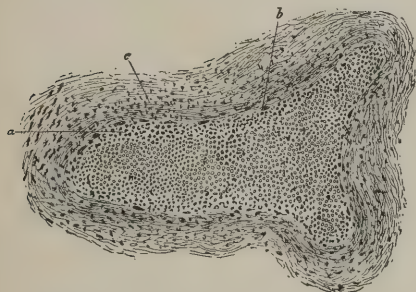


FIG. 48.—Acute inflammation of the mesentery following necrosis of the vermiform appendix on account of the impactation of a fecal concretion: *a*, peripheral accumulation of leukocytes and emigration through the vessel-wall (*b*) and perivascular accumulation (*c*). Hematoxylin and eosin. $\times 175$.

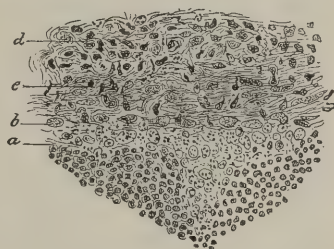


FIG. 49.—The same as Fig. 48, but with higher power: *a*, leukocytes accumulating near the wall; *b*, endothelial line; *c*, leukocytes in the act of passing through the vessel-wall; *d*, perivascular accumulation of leukocytes. $\times 350$.

cement; and Engelmann found that leukocytes may even pass through the bodies of the endothelial cells.

The further movements of the leukocytes outside of the vessels are also of an active nature. They may wander in fairly straight lines to lymphatics, which they have been seen to enter by passing between the endothelial cells (Hering, Heller, Thoma). More frequently they move in a definite direction, as if by a prearranged understanding; this is seen very plainly in the accumulation of leukocytes around the lesion of the cornea in keratitis; in many other inflammations the leukocytes build a wall or ring around some central point.

Chemotaxis.—At first Cohnheim regarded the migration of leukocytes as an active process, but subsequently he coincided with Hering and Schklarewsky in the belief that the cells were merely pressed through the altered walls of the vessels. Taking, however, the facts above mentioned into consideration, it seems that leukocytic emigration is something more than a passive process. This inference has long ago been shown to rest on a substantial basis by the demonstration that chemical substances exert

a profound influence on mobile cells. This influence, which may attract or repel cells, is known as positive or negative *chemotaxis*. Engelmann showed that certain motile bacteria are attracted toward points where oxygen is present. Pfeffer demonstrated that myxomycetes, infusoria, and swarming spores are drawn toward some substances and repelled by others; further, that the power of attraction or repulsion does not bear any relation to the molecular weight or food-value of the substances. Leber, Massart and Bordet, Gabritschewsky, Buchner, and others have made similar observations on leukocytes. It has been shown that the behavior of these cells toward stimulating substances varies greatly, and that chemotaxis plays an essential role in the migration of these cells in inflammation.

The experiments bearing on this point have been carried on by inserting into the tissues of animals capillary tubes filled with certain substances, and then observing to what extent leukocytes would creep into the tubes. Leukocytes are drawn toward the majority of bacteria that induce inflammation, but repelled or destroyed by a few that are especially virulent. Bacterial products also attract leukocytes; and Buchner found that the bacterioproteins—the substances of the bodies of the bacteria—and many of the early products of tissue disintegration exert an attraction upon cells. Leber and others showed that croton oil, turpentine, copper, etc., exert positive chemotaxis; while quinin, chloroform, alcohol, lactic acid, etc., manifest negative chemotaxis. Some of these latter substances were known to suspend ameboid movement (Binz, Pekelharring) before chemotaxis was understood, and they were then referred to as protoplasmic poisons.

Thoma has demonstrated that when the amount of salt in the blood and lymph of the frog is increased to about 3 per cent., the movement of leukocytes and wandering cells is arrested. In warm-blooded animals emigration was stopped by irrigating the mesentery or tongue with a 1.5 per cent. salt solution; the ameboid cells became immobile and globular, and those adherent to the vessel-wall were loosened; but if irrigation was made with a 0.75 per cent. solution, migration and ameboid motion were resumed.

Bouchard, Roger, and Ruffer have shown that the introduction of a micro-organism, such as *Bacillus pyocyaneus*, or its products, into the circulation prevents or delays emigration after the local injection of substances that usually cause marked accumulations of leukocytes; exudation occurs, but the white cells remain within the vessels.

These experiments indicate that the influence of substances in solution varies according to the state of concentration and distribution. The even distribution of bacterial products in considerable quantity in the blood, for instance, may materially diminish the leukocytic emigration toward similar substances collected at a local seat of disease. In some such way may be explained the marked variations in the leukocytic reactions in different inflammations due to the same cause.

Sometimes one variety of leukocytes emigrates in relatively larger numbers than the others, as, for instance, in the skin in dermatitis herpetiformis, in which the eosinophiles gather in large numbers. This indicates that the sensibility toward chemical substances is peculiar for each kind of leukocyte.

The active movements of the leukocytes and wandering cells in inflammation depend, then, on chemotaxis exerted by the diffusible products of bacteria, of tissues, and of other substances. The changes in the vessel-walls, the modification of the endothelium, the vascular dilatation and slow-

ing of the current, and the disarrangement of the corpuscles in the stream, all favor emigration; but the determining factor is the presence of chemotactic substances in the tissues and the vessel-wall, in consequence of which the cells advance, as long as the ameboid motion is intact, toward the points of greatest attraction.

As regards the passage of red corpuscles from the vessels, which may occur to a considerable extent in some inflammations, it is to be noted that it generally succeeds the leukocytic emigration save in those cases in which there is a severe or gross injury to the vessels. White and red cells may be seen lying side by side along the walls of the vessels of the frog's mesentery, but the leukocytes are always the first to emigrate. It is quite clear that the continued active emigration of leukocytes increases the permeability of the walls, so that after a time red corpuscles may be forced through. When the circulatory disturbances become severe, so that stasis ensues, red cells often leave the greatly altered vessels in large numbers, giving the inflammatory exudate a hemorrhagic character.

Phagocytosis.—Metschnikoff introduced the now well-known word phagocytosis to describe the action of cells, especially certain leukocytes and wandering cells, of taking up into their interior pathogenic bacteria and other particles, and of destroying them by a process of intracellular digestion. The leukocytes possessed of this function are the finely granular neutrophile and oxyphile cells (polymorphonuclear leukocytes) and the large mononuclear hyaline cell; endothelial cells and other fixed mesoblastic cells have the same property, but exert it to less degree.

Phagocytosis is largely dependent on positive chemotaxis on the part of the micro-organisms or their products and other substances. The phagocytic leukocytes vary in their action toward different bacteria. Metschnikoff says that in man the hyaline cell does not take up gonococci, which are readily taken up by the finely granular oxyphile cell; this cell does not, however, take up leprosy bacilli, which are engulfed by the hyaline leukocytes. Such differences must depend on varying sensibility on the part of the leukocytes to micro-organisms.

Leukocytes that by virtue of chemotaxis are attracted by bacteria and other particles move toward the bacteria and particles and enclose them in their protoplasm. Subsequently the ingested substances undergo various changes that are ascribed to intracellular digestion. Ferments have been shown to be present in the cells. Leber showed that sterile pus, the result of the accumulation of leukocytes in the anterior chamber of the eye after the insertion of copper, could digest fibrin. Pus-cells, bits of muscle, and other tissue fragments taken up by the phagocytes disintegrate and become dissolved. Ingested microbes present changes in form and in affinity for stains; frequently the degenerating bacteria lie in so-called digestive vacuoles. The exact nature of the bactericidal substances or ferments is not determined.

Metschnikoff concludes that some bacteria must be in a living condition when taken into the cells, because certain bacilli have been observed to perform active movements in the nutritive vacuoles of the leukocytes; again, on introducing leukocytes filled with anthrax bacilli into bouillon the cells fall to pieces, while the bacilli grow rapidly; and it is quite likely that the tubercle and leprosy bacilli found in phagocytes were fully virulent and living when incorporated by the cells. But the incorporation of micro-

organisms by phagocytes does not always or necessarily lead to death of the bacteria; their products may, on the contrary, destroy the phagocytes, so that in many cases the disease progresses rapidly in spite of well-marked phagocytosis. In other cases, as in tuberculosis, leprosy, and glanders, the resisting powers of the bacteria and of the cells are more evenly balanced, and the chronic course as well as the localized form of these diseases has been explained by this peculiarity; in such instances the bacteria may multiply within the cells. The more virulent the bacteria, the less marked, as a general rule, is the accumulation of leukocytes and the phenomenon of phagocytosis. Metschnikoff describes a striking example of the action of bacteria of differing virulence: if an attenuated culture of the bacillus of anthrax is inoculated into the ear of a rabbit, a huge aggregation of leukocytes with vigorous phagocytosis results; but if a virulent culture is injected, an intense serous inflammation follows, the fluid of which contains but few leukocytes—the virulent bacteria repel or kill the leukocytes, the weak attract them. In many instances the ingestion of bacteria or of chemical substances, as arsenic (*Besredka*), is first followed by negative chemotaxis, which later gives way to positive chemotaxis and phagocytosis.

Buchner, as already mentioned, demonstrated that some of the products of tissue disintegration exert marked attraction on leukocytes; this may explain the immigration of leukocytes into practically all areas in which lesions of any kind have produced cell death. The function of the leukocytes in aseptic inflammations, as well as in bacterial inflammations after the active agent has been destroyed or neutralized, is largely to assist in the removal of debris, partly by phagocytosis, partly by carrying the detritus to lymph-nodes and other organs. This is well illustrated in fibrinous pneumonia; after healing begins the peribronchial glands become enlarged and filled with debris from the exudate in the alveoli, brought partly by the lymph-stream, partly by leukocytes migrating from the area involved.

Leukocytes are useful in yet another way, namely, by supplying the formative cells with nourishment; the formative cells under such circumstances appear to act as phagocytes and incorporate the white blood-cells. The question concerning the conversion of migratory cells into fixed-tissue cells is referred to below.

The Extracellular Action of Leukocytes.—While Metschnikoff and his followers looked upon leukocytic emigration and phagocytosis, or the intracellular action of the leukocytes, as the essential element in the inflammatory reaction throughout the animal kingdom, and regarded the vascular, exudative, and other phenomena in inflammation in the higher animals as superadded and auxiliary steps, many facts indicate that this is rather an incomplete conception of the inflammatory process, and that the extracellular action of the leukocytes and the properties of the exudate play at least an equally essential role.

Nuttall was among the first to show that blood-serum has a marked bactericidal effect; attenuated anthrax bacilli, for instance, when placed in normal serum show involution and degeneration forms before they are taken up by phagocytes. This permits the inference that phagocytosis may occur after the inflammatory exudate has reduced the vitality of the bacteria. The demonstration of a microbicidal action of the blood-serum has been abundantly confirmed (*Nissen*, *Buchner*, *Hankin*, *Behring*, and many

others); and further investigations in the same direction have led to results of supreme practical importance in showing the existence of antitoxic substances in the blood of animals immune to certain diseases. But the discussion of the production of immunity—one of the most interesting topics in biology—does not belong here. Certain facts pointing to the local action of leukocytes in producing bactericidal substances must, however, be detailed.

Nuttall and others found that the serum removed from the body possessed more bactericidal power than the blood; Buchner showed that the injection of sterile emulsions of wheat gluten into the pleural cavity produced a sterile exudate remarkably rich in leukocytes and more strongly bactericidal than the blood of the animal, and this bactericidal power was retained after the leukocytes had been killed by freezing and thawing, so that phagocytosis could not possibly play any part. Experiments of similar import, pointing to the production or liberation of bactericidal substances by the leukocytes, have been made by Denys and Havel, and others. Vaughan and Kossel demonstrated the presence in the blood-plasma of nucleinic acid, a bactericidal substance found only in nucleated cells. Löwit was able to extract from leukocytes a strongly bactericidal body, and demonstrated that on ligating the aorta, so as to prevent the entrance of leukoblasts from the hemopoietic organs into the circulating blood, a marked lessening in the bactericidal power of the blood took place with the diminution of polynuclear leukocytes. These facts point strongly to the production of bactericidal substances, or *alexins*, as Buchner calls these protective bodies, by the leukocytes, through a process either of secretion or disintegration. It would seem that in inflammation the emigrating leukocytes, even though they may be destroyed and undergo dissolution, nevertheless hinder bacterial growth by the setting free of bactericidal substances contained in their bodies. Active processes of secretion of alexins on the part of the leukocytes may also occur (Hardy). In these ways the composition and action of the exuded serum may be profoundly changed.

Metschnikoff, while not denying the bactericidal action of blood-serum outside the body, *in vitro*, has persistently maintained that no conclusions can be drawn as to the events that occur in the living organism from the results obtained in experiments with serum outside the body. The pathogenic bacteria, he maintains, are destroyed by the phagocytes. Possibly the serous exudation may serve to attenuate or modify the action of the poisonous chemical products of the bacteria which produce the general intoxication in inflammations. Other observations point to important extracellular processes in the inflammatory reaction. Thus, Afanassieff found that on placing virulent cultures of anthrax bacilli on healthy granulation-tissue a rapid destruction of the bacilli by the serum followed before phagocytosis had time to occur; later the identical degenerate bacillary forms were found outside as well as inside the phagocytes. R. Pfeiffer showed that when cholera spirilla are inserted into the abdominal cavity of refractory guinea-pigs the spirilla become swollen and spheric before phagocytosis has time to occur. Metschnikoff repeated this experiment, and observed that a few minutes after the injection the leukocytes were surrounded by free globular spirilla, a layer of clear fluid separating the cells from the bacteria; here he acknowledges that an extracellular action of the leukocytes takes place.

Furthermore, not all leukocytes are phagocytes. The eosinophiles, or coarsely granular oxyphile cells, never act as phagocytes, yet they are often

present in relatively large numbers in inflammatory exudates. What is their possible function? Kanthack and Hardy observed that on mixing anthrax bacilli with frog's lymph the coarsely granular oxyphiles were attracted and applied themselves to the bacilli; the granules were then discharged, and the bacilli soon showed signs of degeneration and became surrounded by hyaline cells fusing into plasmodial masses which subsequently broke up, the cells containing remnants of bacilli within digestive vacuoles. Hardy has shown that the same phenomena occur on placing *Bacillus filamentosus* in the lymph of the frog. Such observations point clearly to excretory functions on the part of nonphagocytic cells. Kanthack and Hardy found further evidences of this secretory function in various warm-blooded animals as well as in man; similar phenomena were observed in hanging drops of human blister fluid mixed with anthrax bacilli. Hence it may be concluded that the extracellular action of leukocytes is of much importance in inflammation.

Conclusion.—From these considerations it may be concluded that chemotaxis and leukocytic emigration are important and practically constant steps in the inflammatory process; that the action of the polynuclear and hyaline leukocytes is partly phagocytic; that the eosinophile cells are not phagocytic but excretory, and may diminish the vitality of micro-organisms; and that the disintegration of leukocytes increases the bactericidal powers of the serum in the inflammatory area.

The Inflammatory Exudates.—The inflammatory exudate varies in quality and quantity according to the tissues concerned and the nature and intensity of the inflammatory agent. Dense tissues allow but little exudation to take place, while vascular structures without much resistance—*e. g.*, cutaneous and serous surfaces—readily permit much exudation.

The exudates are invariably richer in proteids than ordinary lymph. Whether this is due to increased permeability of the vessel-walls, to the disintegration of cells, or to stimulation of the secretory activity of the endothelium, is an undecided question. The exudates also frequently contain fibrin and its precursors, digestive ferments and peptones, bactericidal substances, and various cells.

The **serous** exudates occur chiefly in milder forms of inflammations, but also in certain very virulent infections; *e. g.*, with anthrax bacilli. The fluid contains little or no fibrin, only a few cells, but more albumin than the transudates. Serous exudates act favorably by irrigating the tissue-spaces and removing or diluting noxious substances; the exudate also brings increased nourishment to the cells, thus favoring reparative cell growth; but in all likelihood its most important effects are attributable to bactericidal substances produced by leukocytes and possibly by other cells (see Extracellular Action of Leukocytes). But the exudate may become a dangerous element in inflammation; it may carry bacteria away from the original focus to adjacent or contiguous structures, such as healthy parts of serous membranes, and through the lymphatics to lymph-nodes, where new areas of inflammatory reaction may be established. Accumulations of exudate in the tissues about the entrance to the larynx may cause asphyxia, and in the spaces of the meninges cerebral compression.

Serofibrinous and **fibrinous exudates** consist, as the terms indicate, either of mixtures of fibrin and serum or almost wholly of fibrin. Such exudates may form in the tissue-spaces, in the serous cavities, and on the

mucous and, more rarely, the cutaneous surfaces. The ferment necessary for fibrin formation is undoubtedly liberated by the disintegration of leukocytes, red corpuscles, and other cells. The fibrin may be precipitated in filamentous and hyaline form from pre-existing serous exudates, or it may be deposited directly upon the tissues at the moment the plasmatic fluid exudes from the vessels; in the latter instance the fluid comes in contact with cells, such as the lining cells, that are undergoing necrosis with the setting free of ferment, the fibrin forming a granular or velvety deposit or a thick membrane on the roughened surface. In serous cavities fibrinous exudates often appear to restrict the spread of the disease. In the peritoneum, for instance, fibrinous adhesions between intestinal coils often confine the infection about the region of its origin, such as the vermiform process or the uterine appendages.

The **hemorrhagic exudate** is due to a considerable diapedesis of red corpuscles, giving the fluid or the tissue infiltrated a bloody appearance. Such exudates signify extensive changes in the walls of the vessels, due either to the intensity of the primary lesion or to nutritive disturbances that have weakened the capillaries.

The **purulent exudate**, or **pus**, is a yellowish, milky or creamy fluid containing many cells, but no fibrin. Its peculiarities are due to disintegration of the proteids, the fibrin, and the necrotic tissue by ferments developed from pyogenic bacteria, as well as from cells. The study of the common pus-producing bacteria outside of the body, in pure culture, has furnished abundant proof of the development of ferments that peptonize gelatin and proteids. Leber showed that copper inserted into the anterior chamber of the eye produced a sterile pus capable of digesting proteids. The cells in the purulent exudate are chiefly polymorphonuclear leukocytes, which are attracted in large numbers by the bacterioproteins of the pyogenic microorganisms (Buchner), by chemical substances, as well as by products of tissue necrosis. Formative cells that succumb to the toxins may also become pus-corpuscles; but in comparison with leukocytes this type of cells takes but a small part in forming pus-cells. As the leukocytes die the cytoplasm becomes granular and fatty, the nuclei are split up into fragments, and complete disintegration may take place. The necrotic tissue and the solid exudate that may have formed in the early stages are liquefied by the proteolytic ferments, and abscess cavities, ulcers, and suppurating wounds result. The pus micro-organisms are to be found in the pus-cells and in the plasma, as well as in the fixed and formative cells, especially in acute processes. The serum of pus contains the same salts as blood-plasma; furthermore, ferments, peptones, and bactericidal substances, and, if old, cholesterol crystals and fat, and also pigment from red blood-cells and from chromogenic bacteria.

The digestive action of the purulent exudate aids in the removal of dead tissue by dissolving and rendering the material susceptible of absorption or separation; but suppuration is to be looked upon as an unfavorable form of infection: it always causes local destruction of tissue and frequently tends to progress.

The Fixed-tissue Cells in Inflammation.—The changes in the fixed tissue in inflammation are partly *retrogressive*, partly *progressive*. These two kinds of changes are often closely associated. In many inflammatory areas the retrogressive changes are found in and near the center,

while proliferation occurs at the periphery. The retrogressive changes are usually more pronounced in the early stages of acute inflammation, while the progressive changes predominate when actual healing begins. There are many inflammations, however, in which cell growth is among the very first phenomena.

The inflammatory agent, of whatever nature—traumatic, chemical, or bacterial—in its first action on the tissue produces certain lesions. There may be necrosis and degeneration of cells; but in order that inflammation may take place the circulation in the vessels must continue. When the primary injury causes immediate death of an area the circulation ceases, reaction cannot take place—dead cells do not react. Hence immediate death in consequence of the primary intensity of the injury is in reality a phenomenon foreign to inflammation; inflammation occurs in the tissue around the necrotic area because here the injury has not suspended the vitality of the cells. It must therefore be apparent that inflammatory reaction follows injuries that produce lesions short of complete necrosis or death of the part.

As the inflammation progresses the fixed cells may be further damaged in various ways. The continued action of the inflammatory agent—*e. g.*, pyogenic and other bacteria—may produce necrosis and necrobiosis of the fixed cells and of the leukocytes. Necrosis may occur on account of the accumulation of toxic chemical products in a tissue the seat of inflammation, on account of the violence of the inflammatory vascular reaction, which may lead to stasis or thrombosis and anemia, and on account of the pressure of the inflammatory exudate that crowds into the tissue-spaces. In milder inflammations the same or similar causes may induce changes in the cells, leading to functional disturbances, and sooner or later to cell death and disintegration. Cloudy swelling and fatty degeneration are frequently observed in the parenchymatous as well as wandering, in new as well as old, cells; when the serous exudate infiltrates a tissue the fluid may soak into various structural elements, such as nerve-fibers and muscle-fibers as well as cells, and cause dropsical vacuoles; mucoid degeneration is frequent, especially in so-called catarrhal inflammations. Degenerations of obscure nature also take place in the intercellular substance, which may change into mucus, or swell up, soften, and disappear. In the myocardium, for instance, the intercellular cement may change so that the muscle-fibers undergo segmentation—*i. e.*, separate into the cells or segments of which they are made up. Hyaline and amyloid degenerations occur in chronic inflammations. Such changes are essentially destructive.

In some inflammations the cell degeneration, like cloudy swelling, fatty and mucoid changes, is associated with proliferation. This is seen in catarrhal inflammations, in which the cells rapidly proliferate and change into mucus. Inasmuch as this mucus has been found to be bactericidal, it would seem as if the proliferation and degeneration in this case favored destruction of micro-organisms.

When the acute changes of inflammation subside, leaving perhaps a defect, as when an ulcer or abscess forms, then the development of formative cells from existing cells occurs for regenerative purposes. But frequently the proliferation in inflammation exceeds in degree and extent and occurs too early to be regarded as purely subservient to repair. Various factors are supposed to initiate this inflammatory proliferation by exercising a more or less direct "formative stimulus" on the fixed cells, especially

those of mesoblastic origin. This is shown by the occurrence of karyokinetic figures in the fixed cells very early after the introduction, for instance, of tubercle bacilli into the tissues (Baumgarten), although it is not established that this is invariably the first result of the action of the bacilli. In experimental inflammations of various kinds, in the cornea and in serous membranes, evidences of enlargement and of multiplication of the fixed cells also appear (Leber, Ranvier). Changes in the physical and chemical properties of the cells and the intercellular substance may induce cell multiplication. The bathing of the cells in a richly nutritive exudate and the presence of numerous leukocytes are conditions that may be regarded as favorable to cell growth.

In typhoid fever a marked proliferation occurs in the endothelial cells of the lymph-follicles of the intestine, mesenteric lymph-nodes, and spleen; and the new cells acquire marked phagocytic properties, as shown by their taking up other cells (Mallory); this is seen also in other diseases.

The young tissue that develops in inflammatory proliferations, such as the so-called infectious granulomatous processes (tuberculosis, syphilis, etc.), and also in the latter stages of acute inflammations, as in the healing of a suppurating wound, is commonly known as granulation-tissue.

When such tissue is examined microscopically various forms of cells are seen:

1. Small round cells, with deeply stained, irregular, lobulated, and horseshoe-shaped nuclei—polymorphonuclear leukocytes—which take no active part in the formation of new tissue; many are apparently consumed by the formative cells.

2. Cells of variable size, with round or oval, rather faintly staining nuclei and oval, spindle-shaped or branching bodies—formative cells derived from pre-existing cells.

3. Multinuclear giant cells; these occur in granulation-tissue of bacterial origin, such as tuberculous proliferations; also in wounds, around necrotic material, and about foreign bodies. Their origin is variously interpreted: from the confluence of leukocytes (J. Arnold, Ziegler, Metschnikoff), or from that of epithelial and formative cells; from fibroblasts by multipolar or multiple mitosis, or nuclear fragmentation without division of the body (Virchow, Weigert); from endothelial cells, etc. The tendency is to regard giant cells in infectious processes as phagocytes; when developed in the vicinity of foreign bodies of various kinds their function is clearly one of absorption and removal. When their function is fulfilled multinuclear giant cells may split up into small cells.

4. Among the various cells are also found some that cannot be distinguished morphologically or otherwise from large mononuclear hyaline leukocytes. While the researches of Ziegler, Nikiforoff, Marchand, and many others have led to the general opinion that the leukocytes cannot form fixed cells, uncertainty still obtains as regards the large hyaline variety. The cell is not distinguishable from fibroblasts in one stage of their growth. Metschnikoff attributes to this cell the power to change into connective-tissue cell. He claims that in the tadpole and other lower animals the development of leukocytes into fixed cells can readily be traced; and he and his pupils lay more stress on the part taken by leukocytes in the inflammatory tissue formation than others who have studied this problem. J. Arnold injected into the circulation small foreign bodies, around which the leuko-

cytes formed a wall; later the bodies became attached to the wall of the vessels and enclosed in a capsule of connective tissue formed by cells the origin of which he is inclined to trace to the large mononuclear leukocytes. However, the question whether the large hyaline leukocytes can become fibroblasts must still be considered open.

5. Small lymphocytes and plasma-cells. In practically all cell accumulations of inflammatory origin cells occur with dense, round, deeply staining nuclei and a small rim of protoplasm—the small lymphocytes. Unna has shown that many inflammatory infiltrations contain in varying numbers a peculiar cell, the protoplasm of which stains blue with methylene-blue, while the nucleus, usually eccentric in its situation, stains more lightly and appears as a clear spot with a few irregular chromatin masses scattered along the nuclear membrane and in the interior. This is the *plasma-cell*. Its shape varies under different conditions; it may be pear-shaped, oval, or elongated. In suitable preparations the shape, the somewhat granular or broken-up cytoplasm, and the characteristic nucleus render this interesting cell easily recognizable even in sections stained with hematoxylin, which gives the cytoplasm a faint bluish tinge. Most writers (von Marschalko, Councilman, etc.) believe that the plasma-cell originates from locally pre-existing or emigrated lymphocytes. Others consider them emigrated large mononuclear leukocytes, the protoplasm of which has undergone nutritive changes, causing it to be basophile. Mitotic figures indicate that plasma-cells may multiply (Councilman). Many so-called round-cell infiltrations are made up largely of plasma-cells. The special significance of the plasma-cell has not yet been discovered; the cell is not phagocytic. There is also division of opinion as to its fate; Krompecher and others claim that it can form mature connective tissue, but this is by no means definitely established. Its occurrence in normal lymphatic glands and in the spleen has been noted.¹

Another peculiar cell of unknown origin and significance is the “mast-cell” (*Mastzelle*), also found in the outskirts of inflammatory areas and elsewhere, though in small numbers. It is characterized by the presence in the protoplasm of numerous small basophile granules, which stain red with methylene-blue; such granules are said to be metachromatic.

THE LOCAL AND GENERAL SYMPTOMS OF INFLAMMATION.

The external manifestations of acute inflammation are commonly redness, swelling, heat, and pain (rubor, tumor, calor, dolor). These are the so-called Galenic signs of acute inflammation, and the primitive definition of the process included only those states in which these cardinal symptoms are present. But inflammation may exist without any of these gross signs, so greatly has the significance of the term inflammation changed since its introduction by Celsus. To the four original cardinal signs mentioned has been added a fifth, the loss or disturbance of function (*functio læsa*); this symptom may be said to be constant.

The redness of inflammation is due to arterial, and especially to venous and capillary, hyperemia. The swelling depends upon several factors—namely, hyperemia, exudation of serum, emigration of leukocytes, and, if the process has existed for a little time, upon the production of new tissue. The pain is ascribed to the tension and the pressure upon the nerves as well

¹ For literature on the plasma-cell, see *Progressive Medicine*, p. 247, March, 1899.

as to the direct changes in the nerve-filaments; it is subject to much variation, being generally acute where the tissue is subjected to great tension.

The temperature of the inflamed area in superficial regions may be raised above normal, but it never exceeds the temperature of the interior of the body. The higher temperature is due to the increased amount of blood that passes through the area, in consequence of which more heat is brought to the surface (John Hunter). In inflammation of the internal organs the rise of the temperature above normal is immaterial as compared with the temperature of normal internal organs taken at the same time. The fever that often accompanies inflammation has nothing to do with any local increase in heat-production. When stasis or extensive necrosis occurs in inflamed areas the local temperature may fall (Cohnheim).

The loss or disturbance of function consequent upon inflammation depends on the change in the structure and in the chemicophysical conditions of the tissue involved; and the degree and danger of the resulting functional interference will depend on the kind and the extent of the inflammation, upon the physiologic importance of the inflamed tissue, and upon a number of local conditions that are best understood from the descriptions of inflammations in the special organs given in subsequent chapters.

The consideration of the general symptoms that develop in the course of many inflammations does not belong here. Inflammation is a purely local process. The term does not include the changes in the organism at large, the fever, the general intoxication and infection, directly or indirectly associated with many forms of inflammation. Local inflammation may be accompanied by severe constitutional symptoms and changes due to the absorption by the blood and the lymph of the toxic products of pathogenic micro-organisms and of disintegrating tissue and exudate. Bacteria and tissue-fragments may enter the general circulation, and, lodging in internal organs as emboli, give rise to secondary or metastatic processes. These important problems, as well as the changes that occur in the blood at large in various inflammations, are discussed elsewhere.

THE FORMS OF INFLAMMATION.

Inflammation appears in various forms, depending on the tissue involved, the nature and intensity of action of the inflammatory agent, and upon other conditions. An etiologic classification, which would be the most desirable, is hardly possible, because the same agent may give rise to different forms of inflammation and different agents to the same forms. A classification depending on the anatomic nature of the changes and of the exudate also meets with difficulties, because the inflammatory process presents manifold peculiarities and variations according to the structure, function, and position of the tissue it involves.

Inflammations may be grouped in a general way according to the nature of essential causes: traumatic, thermal, chemical or toxic, and infectious.

Traumatism produces inflammation in various ways. The mechanic trauma as such may cause passive alterations in the vascular wall and disturbances of the vasomotor innervation favoring exudation and the emigration of leukocytes, which are attracted by the chemical products that arise from dead cells and from extravasated blood in the tissue-spaces. Undoubtedly the most important role played by trauma as an inflammatory agent consists

in causing breaks in the coverings of the mucous and cutaneous surfaces through which micro-organisms gain entrance.

Thermal influences—heat and cold—cause inflammation by direct changes in the tissues when their action is of moderate intensity and transitory or brief duration. More prolonged action results in diffuse necrosis, followed by reactive inflammatory phenomena around the dead tissue, absorption, and repair.

Chemical substances—as mineral acids, alkalies, many salts, etc.—cause, when acting in great concentration, complete and instantaneous necrosis of the tissues, so that inflammation appears only at the margins of the necrotic tissue. There are also chemical substances the action of which is more selective. Here belong the substances that attract leukocytes, so as to cause suppuration, and also many dilute acids, alkalies, and salts, cantharides, etc., which may produce inflammatory lesions at the point of primary contact as well as at the point of elimination, *e. g.*, the intestinal mucous membrane and the kidneys. Toxic substances may arise in the interior of the body in consequence of abnormal metabolism, and cause acute and chronic inflammations, as in gout and uremia (uremic pericarditis). Many forms of dermatitis are now regarded as due to auto-intoxication of this kind.

The infections are the most important causes of inflammation. The reactive tissue-changes in consequence of bacterial lesions assume many forms, but they are characterized especially by a more or less well-marked progressive tendency depending upon the production of new generations of bacteria and new doses of toxic substances. Bacteria may cause inflammation in the skin and elsewhere, due to direct infection from without; or they may be carried by the lymph and blood and cause inflammation in the internal organs. The toxic substances produced in local bacterial inflammations are often absorbed by the blood, and cause general toxic symptoms and inflammatory changes at the place of elimination and elsewhere. On this account and because of their progressive tendency the infections give rise to the most important inflammations from a practical standpoint; they are also the most frequent.

The classification of the infectious inflammations in a simple manner is not possible except in the most general way. The form of the inflammation caused by a given organism is not constant. The modifying influence of the relation between the resisting power of the cell and the virulence of the micro-organisms may be recognized in all infectious inflammations. Attenuated anthrax bacilli in a susceptible animal or virulent bacilli in a refractory animal may lead to local suppuration; while virulent bacilli in a susceptible animal causes rapid serous exudation without leukocytic accumulation, and a general septicemia. Tubercle bacilli may give rise to a variety of forms of tuberculous inflammation. Under varying conditions the same micro-organism may cause various forms of inflammation that merge insensibly one into the other, and which are described in detail in the sections dealing with the pathologic anatomy of the organs.

Anatomically the various forms of inflammation depend on the character of the exudate, the amount of the leukocytic emigration, and the extent and nature of the changes in the fixed tissues. As already indicated, these anatomic forms are far from being etiologic entities.

According to the character of the exudate, inflammations are divided

into *serous*, *fibrinous*, *hemorrhagic*, and *purulent*, with combination forms, as *serofibrinous*, *fibrinohemorrhagic*, *seropurulent*, etc. The manner of formation of the inflammatory exudates has been discussed. The exudation may form in the tissue-spaces, the lymph-vessels, and on the surface of serous and mucous membranes. If the serous exudate accumulates in the spaces of a tissue, the condition sometimes is called inflammatory edema. Inflammations of mucous membranes accompanied by serous exudation, the formation of much mucus, and desquamation of epithelial cells are called serous catarrh, seromucous catarrh, and desquamative catarrh; when mucus predominates the inflammation is designated catarrhal.

Inflammations of mucous membranes accompanied by the formation of fibrinous exudates are frequently called **croupous**. The fibrinous layer usually forms where the epithelial lining has been destroyed, so that the connective tissue is exposed; from such places the membrane may spread over the epithelium, as yet intact. In the familiar disease, croupous, fibrinous, or lobar pneumonia, which is caused by the *Micrococcus lanceo-*

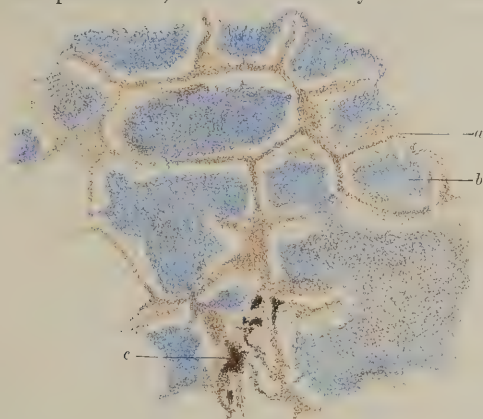


Fig. 50.—Fibrinous inflammation of lung: *a*, wall of alveolus; *b*, alveolus filled with fibrinous exudate; *c*, coal-pigment. Weigert's fibrin stain. $\times 125$.

latus, there is formed in the alveoli a network of threads of fibrin enclosing in the meshes various kinds of cells (Fig. 50). Upon mucous membranes, such as the pharyngeal or laryngeal, fibrinous inflammations form removable membranes, and are usually caused by the diphtheria bacillus. The vapors of strong chemicals, like ammonia, also induce fibrinous inflammations.

Suppurative inflammations and the resulting abscesses and ulcers are generally caused by the so-called pyogenic or pus-micro-organisms. The number of bacteria that may produce positive chemotactic substances, so as to lead to pus formation, is very large. In addition to *Staphylococcus* and *Streptococcus pyogenes* and other less common pyogenic micro-organisms, it has been shown that the gonococcus, typhoid bacillus, *Bacterium coli commune*, *Micrococcus lanceolatus*, *Bacillus mucosus capsulatus*, *Micrococcus tetragenus*, *Bacillus proteus*, ray-fungi, and others may lead to suppuration. Chemical suppuration independently of bacteria is now a well-established fact. This form has only a limited clinical interest; it heals readily, does not tend to spread or to cause metastatic abscesses; the cause does not

reproduce itself. Among chemical, positively chemotactic substances the following are capable of producing pus: mercury, turpentine, petroleum, dilute croton oil, 5 per cent. to 10 per cent. solutions of silver nitrate, calomel, creolin, digitonin, digitoxin, and the oils of cajuput, cloves, juniper, mustard, savin, etc. (Councilman, Uskoff, Steinhaus, Janowski, Leber, and others).

The development of suppurative inflammation may be studied well in the so-called miliary abscess due to implantation upon the walls of capillaries of micro-organisms carried as emboli in the blood-current. The bacteria, or rather the toxic substances produced, first cause necrosis or necrobiosis of the cells with which they come in contact, shown microscopically by the absence of the nuclei and the indistinctness of the outlines of the cells around the microbial colony. Soon vascular changes occur with leukocytic emigration (Fig. 51); the leukocytes are attracted toward the toxic substances, and form a zone around the dead cells and the bacteria. Here they are directly exposed to the poisons produced by the latter, and those that have moved nearest the center of microbial activity and perhaps

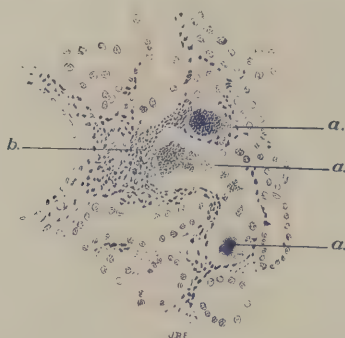


FIG. 51.—Acute ascending nephritis, secondary to cystitis, and caused by *Staphylococcus aureus*: *a*, micrococcal colonies in uriniferous tubules, the epithelium of which is necrotic; *b*, polymorphonuclear leukocytes accumulating about the microbes. Hematoxylin and eosin. $\times 125$.

incorporated bacteria are soon killed. The emigration continues and the central destruction extends. The ferments produced by the bacteria and by the cells liquefy the dead tissue; the exudation from the vessels does not coagulate, and there is produced a turbid, grayish liquid, or pus, which contains leukocytes—pus-cells or pus-corpuscles—in large numbers. The resulting cavity, or abscess, which was at first microscopic in size, may extend in the manner indicated, or coalescence of several abscesses may give rise to large cavities.

Suppurative inflammation in any tissue, due to direct infection from without or from the blood or lymph, begins essentially in this manner. When the pus becomes a little older the cells undergo albuminous and fatty changes and necrosis, and the fluid assumes a yellow, cream-like color. In the meantime the fixed cells around the focus proliferate, and a layer of formative tissue is produced, which becomes infiltrated with leukocytes. The inner layers of this wall undergo gradual disintegration, while on the outside new tissue is constantly being formed from the old, so that finally a distinct wall or capsule is produced.

During the development of such changes in the skin or subcutaneous tissue there is excellent opportunity to study the cardinal signs of inflammation—the redness, swelling, heat, and pain.

The further fate of an abscess varies. The pus may putrefy, due to a mixed or secondary infection with saprophytic bacteria. The cavity may be opened by the surgeon or it may open spontaneously; the process extends diffusely if the contents flow out on a serous membrane or into loose tissues; or the micro-organisms may die, the contents becoming sterile. More or less complete absorption may follow, with cicatrization and perhaps calcification.

When the pus micro-organisms are relatively virulent the suppurative inflammation may assume a spreading or diffuse form, giving rise to indistinctly circumscribed purulent infiltrations (called phlegmons) or to diffuse suppurative exudates on serous membranes. In mucous membranes suppurative inflammation may remain superficial, causing mucopurulent exudates, epithelial desquamation, and necrosis.

Diphtheric inflammation is characterized by coagulation necrosis of the inflamed tissue, which with the plasmatic exudate forms an adherent fibrinous layer (Fig. 52). The terms diphtheric inflammation and diphtheria are not synonymous. Diphtheria is caused only by the diphtheria bacillus,

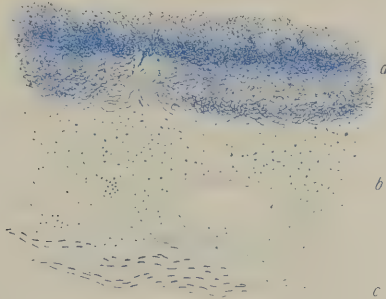


FIG. 52.—Diphtheric esophagitis, due to the diphtheria bacillus: *a*, mucous membrane which has undergone coagulation necrosis and formed a fibrinous network; *b*, swollen and infiltrated submucous coat; *c*, muscular coat. $\times 125$.

while diphtheric inflammations, unfortunately so called, may be caused by a number of other micro-organisms than the diphtheria bacillus, and also by chemical and thermal agents.

It would be much better to confine the terms diphtheric and diphtheria exclusively to the changes produced by the diphtheria bacillus.

This form of inflammation occurs especially on the mucous membranes of the pharynx, intestines, urinary bladder, and the vagina, as well as on the skin. The necrosis may involve only the superficial layers of the epithelial covering, the cells of which lose their nuclei and are changed into irregular flakes; or it may involve the subepithelial connective tissue as well, the dead tissue together with the exudate being converted into a granular, hyaline, or fibrinous layer, quite firmly attached to the underlying structures; if it is torn away, it leaves a ragged surface. The necrotic and coagulated material presents a whitish, grayish-white, or yellowish appear-

ance, which in the intestine may become green or brown from staining with bile and intestinal contents. Later the deeper layers may soften, the membrane after its detachment leaving a distinct loss of substance.

Productive inflammation is characterized by the formation of new tissue. The term is applied to forms of inflammation in which the production of new tissue seems to stand in direct relation to the inflammatory agent, and to cases in which the new tissue appears to be produced for the purposes of regeneration or replacement of old tissue. Distinction between purely regenerative proliferation and proliferation due to direct stimulus of the inflammatory agent cannot always be carried out. Generally speaking, the new tissue formed in productive inflammations is connective tissue, which presents itself in the early stages of its existence as formative tissue, or granulation-tissue, subsequently undergoing either various kinds of degeneration, or changing into mature, fibrillated connective tissue with the tendency to shrink and contract (cicatrical tissue). A distinct group of productive inflammations is that caused by certain micro-organisms which produce progressive formations of granulation-tissue with a more or less well-marked tendency to necrosis. It includes the productive inflammatory changes in various tissues produced by the specific micro-organisms of tuberculosis, syphilis, glanders, rhinoscleroma, and actinomycosis, and certain blastomycetic and protozoan processes in the skin and elsewhere. In this group of inflammations, the *infective granulomas*, the inflammatory exudation and leukocytic emigration are usually not so well marked or of late occurrence; but it is not to be forgotten that the bacillus of tuberculosis, for instance, may cause acute exudative inflammations. In mucous membranes productive inflammatory changes may lead to a general hyperplasia of all the structures in the mucosa, while in other cases the overgrowth may involve only some of its constituents, as, for instance, the lymph-nodes in the nasopharyngeal and intestinal mucous membranes. Productive inflammation following mere physical irritants is observed in the lungs in the chronic proliferation of the connective tissue that follows the inhalation of coal-dust and fine silicious particles. Condylomas and warts in the skin, osteophytes, and hyperostosis of bones are additional instances of purely inflammatory proliferations arising in various conditions, and due apparently to direct stimulation of the cells or caused by increased nourishment on account of the hyperemia and the exudation. Another important group of chronic productive inflammations is that characterized by a degenerative atrophy of the specific cells and hyperplasia of the connective-tissue stroma of organs like the liver, the kidney, the stomach, etc.—the so-called *chronic interstitial inflammations* (cirrhosis of the liver, chronic interstitial nephritis). The essential changes are degeneration and necrobiosis of the glandular cells, leukocytic infiltration and proliferation of the connective tissue, with the obliteration of old and the formation of new vessels, and usually contraction of the new tissue, leading to induration and shrinking of the organs. The question whether the degenerative changes in the parenchymatous cells are primary and the growth of connective tissue consecutive, or whether the connective-tissue hyperplasia is primary and the parenchymatous degeneration secondary and due to the increasing contraction of the new-formed fibrous tissue, cannot be said to have as yet received definite answer. It is probable that either process may be the starting-point. Of late, however, and more especially since the importance of chronic intoxications and auto-

intoxications has become more fully recognized, the opinion has grown stronger that many such diffuse productive inflammations are due to primary parenchymatous degenerations and necrosis, consecutive to which the tissue of the stroma undergoes hyperplasia (Weigert, Ackermann, and others). Flexner has demonstrated the development of chronic interstitial changes in the liver secondary to degeneration and necrosis produced by the experimental introduction of toxic substances.

In connection with necrosis, infarcts, degenerations, and thrombosis it was stated that new connective tissue may in time replace the necrotic, atrophic, and useless material. Inasmuch as inflammatory exudation and leukocytic emigration are occasionally observed around such areas during this process, it is also warranted to regard such replacement fibrosis (Adami) as of inflammatory origin, as a species of productive inflammation intended to repair injury and remove useless and noxious material.

THE TERMINATION OF INFLAMMATION; RESORPTION; THE HEALING OF DEFECTS AND OF ASEPTIC AND SUPPURATING WOUNDS.

The individual inflammations present many variations as regards course and termination, depending upon the special cause and upon local and general conditions of the organism. The reparative and counteracting tendencies of the inflammatory process proper are far from being wholly and immediately victorious. Necrosis, suppuration, the accumulation of exudate, are results which, as the causes of inflammation subside, lead to resorption and repair. Productive inflammations with the development of cicatricial tissue lead to contraction and induration which seriously interfere with functional activity.

Acute inflammatory reaction due to influences of brief duration and only moderate intensity are often followed by rapid restitution; but a prolonged bacterial infection associated with necrosis, severe vascular changes, and much exudation requires a long time for definite repair. The removal of the exudate, of the necrotic material, as well as of foreign bodies, is accomplished by means of lymphatic and venous absorption, aided by digestion and by phagocytosis on the part of leukocytes, formative cells, and giant cells. A mild degree of chronic inflammation persists around many necrotic masses and exudates until their complete removal is accomplished. Serous exudates are quite rapidly absorbed by the lymphatics and veins. Fibrinous exudates as well as pus require a longer time; the fibrin must first be redissolved; in many inflammations of this kind, especially when some form of obstruction, such as pressure or thrombosis, delays venous and lymphatic absorption, the exudate may become inspissated, infiltrated with lime salts, and closely surrounded by new fibrous tissue. Emigrated leukocytes that have remained active may, during resorption, immigrate into the lymph-vessels or aid actively in the removal of the dead material. Necrotic tissue situated superficially is loosened by digestion and phagocytosis from the healthy and allowed to drop off (sequestration, demarcating inflammation); solid necrotic masses in the interior are gradually absorbed and replaced with living tissue or encapsulated, undergoing later perhaps calcification or softening. As already stated, necrotic tissue and exudate may attract leukocytes and embryonal cells, which take up in their interior bacteria, pigment-granules (pigment-carrier cells), remnants of cells and tissues that

have undergone necrosis and fatty as well as other changes (granule-cells); these substances may be dissolved by intracellular action or carried to the regional lymph-nodes or the internal depots for the removal of useless materials. Some of the leukocytes are taken up by formative cells, which in this manner receive food. Necrotic masses as well as foreign bodies may become surrounded by granulation-tissue in which lie multinucleated giant cells that assist actively in the removal of the foreign material, on the surface of which they produce small depressions. The regeneration of the dead cells is accomplished according to the principles of regeneration in general; extensive necrosis, the death of highly specialized cells, such as ganglion-cells, and infected wounds are not followed by perfect regeneration, but by an inferior species of repair, namely, cicatrization. Cicatricial or scar-tissue is granulation-tissue or formative tissue that has changed into a finely fibrillated tissue with few vessels and few small cells.

Many exudative inflammations of serous membranes terminate in the growth of new fibrous tissue that leads to permanent adhesions of apposed surfaces or to localized fibrous thickenings. This new growth follows destruction of the endothelial cells and of the subendothelial connective tissue. Granulation-tissue forms about necrotic masses, abscess-cavities, and foreign bodies; as absorption takes place it substitutes the material removed and changes into a scar, or it forms a fibrous capsule around the calcified or softened detritus that remains unabsorbed.

Healing of Aseptic and Suppurating Wounds.—The underlying factors are the same in the healing of all wounds and defects, inasmuch as new tissue is always necessary even when the margins of an aseptic incised wound are held in perfect apposition. Healing of aseptic incised wounds which is accompanied with a minimum and, to the surgeon, invisible amount of granulation-tissue, is known as healing by primary union or first intention.

The best conditions for primary union are obtained when the margins of the wound are least injured, when infectious and toxic influences are reduced to a minimum, and when perfect apposition is secured. The primary injury—the incision—leads to some bleeding and to the oozing from the tissue-spaces of a little serum, which coagulates into a fibrinous layer, gluing the margins together. Then follows a mild inflammation in the margins of the wound. The exposure to the air, the solutions employed in dressing the wound, the substances in the extravasated blood, the dead or maimed cells, all combine to produce substances that attract leukocytes. Moreover, a mild infection cannot always be excluded, even in a clinically aseptic wound. The vessels dilate and a little serous exudation occurs. These changes favor healing; the leukocytes remove dead material, while the serum and the leukocytes increase the nourishment of the formative cells. In the meantime the fixed cells divide, formative cells lie in the tissue-spaces on each side of the wound as well as between the margins; new capillaries may form; the fibroblasts secrete a homogeneous or fibrillated intercellular substance that definitely holds the margins together, while the surface becomes covered with new epithelial cells. The final result is a small strip of connective tissue which with time becomes almost indistinguishable from the surrounding tissue. In favorable cases the papillary layer of the skin is almost wholly reproduced, so that the site of the wound may become nearly invis-

ible; otherwise the wound is marked by a flat, smooth line, at first red, but subsequently whitish.

The healing of open wounds is accomplished with visible granulation-tissue, and is called healing by secondary union or by second intention. This form of healing may occur with or without infection. In an open, non-infected wound the course of healing may be outlined as follows: After twenty-four hours the margins and the floor are red and swollen; a few shreds are seen, and there is a slight amount of grayish exudate present; on the second day the individual tissues are no longer recognizable; the tissue is soft and grayish red, and a reddish-yellow fluid covers the surface; the margins of the wound and the tissue immediately adjacent are red; the exudate contains many leukocytes. A mild inflammation of the floor and margins exists. But already on the third or fourth day small red nodules are visible beneath the exudate, which soon coalesce and form a red, granular surface—"the granulation-surface"—due to the formation of new vessels and of embryonal tissue. Leukocytes are especially numerous in the upper strata of this tissue. Afanassieff has shown that the serum in granulation-tissue is markedly bactericidal, and that virulent anthrax bacilli placed on healthy granulating wounds are destroyed, and do not produce a general infection, so that granulation-tissue forms a protective layer against microbial invasion.

The fibroblasts and capillaries proliferate until the defect is filled; intercellular substance is produced; the walls of the new capillaries become thicker; the hyperemia ceases as the wound is covered with new epithelium derived from the cells at the margin. As the granulation-tissue is transformed into scar-tissue many of the new vessels are closed; others contract their lumen, so that the vascularity diminishes. The subsequent shrinking of the cicatricial tissue may lead to serious distortions in the case of large defects healed in this way.

Practically a similar process takes place in the healing of suppurating wounds; here the course may be greatly delayed and disturbed by the continuous death of the surface of the granulation-tissue on account of the action of the micro-organisms; or there may occur a more luxuriant and erratic development of embryonal tissue without leading to the formation of scar-tissue. Luxuriant and persistent growth of granulation-tissue is frequently observed when foreign bodies, such as pieces of cloth or sutures, lie at the bottom of the wound, or when suppuration, and especially when tuberculousis, is present. Otherwise the growth of new tissue ceases when the defect is closed, according to the general law governing the processes of regeneration, that the amount of tissue to be produced is determined by the functional necessities in each case. When the development of granulation-tissue (and the resulting fibrous tissue) for unknown reasons passes beyond normal bounds and pays no heed to physiologic laws of growth, large masses of scar-tissue may result, that are known as keloids.

CONCLUSION.

The definitions and theories advanced from time to time in explanation of inflammation are very numerous and often contradictory. In recent years it has become more and more evident that the only theory that allows the full meaning of inflammation to be grasped is the broad, biologic conception which recognizes in inflammation an adaptive, protective, and repar-

ative tendency common to the reactions to injury among all animals. It is in a large measure to Metschnikoff that pathology owes this broad conception concerning the significance of the natural phenomena of inflammation. It is probably not practicable to frame a concise definition of inflammation in which the exact part played by each factor can be fully indicated. The definition must be general; the moment phagocytosis or any other single phenomenon is emphasized to the exclusion of others, the notion of inflammation, its meaning and tendency, is liable to become one-sided and obscure.

It has been pointed out in the preceding pages that inflammation brings into operation a number of factors to counteract harmful agents, protect the organism at large, and effect healing. The common mode of origin, the similarity of the changes (though combined in differing proportions), and the evident tendency of the inflammatory processes to protect and repair, justify fully the teaching that inflammation is essentially an adaptive, protective, and reparative process, a means of self-preservation. Yet it must not be forgotten that the mechanism of defence and preservation is far from perfect; the exudate may possess but little bactericidal power; the phagocytes may be powerless, or the bacteria may multiply freely within them, as in tuberculosis; extensive destruction of tissue may occur before the virulence of the bacteria is neutralized; general infection and intoxication may cause death; the fixed cells may form imperfect material for repair or multiply in excess; the resulting cicatricial tissue may lead to serious functional disturbances. The inflammatory reaction does not respect the relative importance of the tissues: thus, violent inflammatory exudation may cause occlusion of the larynx, or, in the meninges, cerebral compression, and the fibrous tissue produced in repair after endocardial infection may produce valvular disease. These disastrous consequences cannot always be regarded as unavoidable in order that inflammation may fulfil its primary purpose. Hence inflammation, though biologically an adaptive and preservative process, may appear harmful to the physician, requiring the intervention of medical art. Taking all things into consideration, we may conclude that inflammation is a reaction to local injuries, calling forth protective and reparative measures; but that it is an imperfect pathologic adaptation, often leading to consequences that are dangerous *per se* and defeat its purpose.

TUMORS.

Introduction.—Modern ideas concerning the pathology of tumors may be said to have begun with the publication of Virchow's *Die krankhaften Geschwülste* in 1863. At this time, with the basis furnished by the cell doctrine, the knowledge of tumors was rescued from the chaos into which previous speculation had brought it. Since the time of Virchow's classic production a vast amount of information upon tumors in their various aspects has been recorded, and to this fund of knowledge each passing year makes its contribution. Paradoxical as it may seem, however, our increasing knowledge has in certain directions only served to make more confusion, and in one particular direction, viz., as regards the *cause* of tumors in general, speculation is as rife and almost as fruitless as it was before the modern era. Etiology is the only certain guide to perfect conceptions of pathologic processes, and with etiology obscure, as is the case with the true tumors, we grope in the dark when attempting to solve many of the problems presented in their life phenomena.

Definition.—Without a clear conception of all the factors which lie at the beginning of tumor formation, it is not possible sharply to define them. How difficult the matter of definition is can be best illustrated by noting the fact that almost every prominent authority upon tumors has given a definition differing from that of others working in the same direction. With so many aspects as the study of tumors presents, each author has attempted to define from the particular phase of the subject into which his individual studies have taken him. When it can be said of this or that variety of tumors that it is due to such and such a cause, as we say of tuberculosis that it is the disease consequent upon the invasion of the tubercle bacillus, definition will define. Until then no single definition can cover the ground.

In the larger and more common forms, tumors are familiar objects to all as localized swellings in various portions of the human body. Not every localized swelling is a tumor, however, and the veriest tyro in medicine would have no hesitation in separating the reddened or fluctuating swelling of an acute abscess, or the mass of overdeveloped muscle on a blacksmith's arm, from a cancer of the breast. But all tumors are not large; many are almost or quite microscopic in size. Neither are all tumors localized swellings, for they may grow very diffusely. Further, while the differentiation of an acute abscess and a well-marked tumor is not difficult, there are firm, localized swellings arising from pyogenic, tuberculous, syphilitic, and other infections that partake of many of the characteristics of true tumors.

The aim of definitions is particularly the discrimination of true tumors, or neoplasms, from such formations as result from hypertrophy or hyperplasia, from the infective granulomas, and from other peculiar pathologic deposits or growths. How difficult the task really is can be best appreciated by a survey of the voluminous controversial literature bearing upon this topic.

A definition, however, even though imperfect, furnishes a center about which our ideas may crystallize, and such a definition is acutely demanded for tumors.

All true tumors are new growths of tissue, the elements of which pre-exist in the body. They are independent new growths, or, as Thoma has happily styled them, "autonomous" new growths. Their characteristics, as now understood, are most clearly set forth by Lubarsch, whose *résumé*¹ upon the subject of these neoplasms is the most recent and comprehensive now available, and his propositions may be provisionally accepted. They are as follows:

1. In the present state of science, autonomous new growths may be defined as growths that arise often without demonstrable cause and conform more or less to the structure of the mother-tissue, but which with regard to form are atypical, and functionally either differ qualitatively from normal tissues or by reason of their anatomic structures have a function of no value to the body.

2. The classification of these new growths is best based on histogenetic and physiologic principles.

3. It is at present impossible to give a single comprehensive explanation for the formation of these tumors.

Classification.—The imperfect state of our information concerning the ultimate causes of the various forms of tumors makes the matter of classification difficult; and while numerous systems have been proposed, the test of increasing knowledge has shown weak points in them all. Since tumors spring from the elements of organs and tissues of the body, it is to be expected that they will retain more or less perfectly a morphologic affinity with the parent-tissue. This is the case with many kinds of neoplasms, and in consequence a basis for classification is furnished which, if not perfect, at least serves for descriptive purposes. It is this histogenetic basis that Lubarsch refers to in his second proposition; and since Virchow's classic publication upon tumors it has been more or less liberally applied. Certain kinds of tumors, as we shall learn, do not retain the impress of their parentage, and such tumors are separately considered upon the basis of their peculiar physiologic characters. The terminology of most tumors, as at present adopted, is essentially a morphologic one, founded upon our notions of the histogenesis of tumors. Thus, a tumor composed of muscle-elements is a myoma; one composed of neuroglial elements a glioma or neuroglioma; and so on, as will be seen when the separate varieties of tumors are discussed. Two great varieties of new growths with special life phenomena are represented by the sarcomas and the carcinomas. It must not be forgotten, however, that the present classification and terminology are largely artificial; and that insensible gradations occur which unite the varieties of tumors so as to leave no definite line of separation.

MORPHOLOGY OF TUMORS IN GENERAL.

Anatomic Features.—The variations of neoplasms in *size* is a well-known characteristic. A tumor may be so small as to be only visible to the eye; indeed, the nodule may even be so minute as to be detected only by the most careful microscopic examination. Again, it may reach

¹ *Ergebnisse der allgemeinen Pathologie und pathologischen Anatomie*, ii., 1895, 1897.

an enormous size, as seen in ovarian tumors, which may become larger and heavier than the body in which they originate.

There is no constancy in the *shape* assumed by tumors, although there is a general tendency for these formations to take a spheric form. All gradations from more or less spheric to flat masses may be encountered. The shape of the tumor-mass is often influenced by its surroundings, those growths springing from free surfaces tending to extend symmetrically, producing rounded forms, while those which are confined often assume the configuration of the cavity in which they lie. A whole organ may become filled with a new tumor-growth, while other growths spontaneously take an organoid form, so that it sometimes becomes possible to detect a distinct resemblance between a tumor and one of the viscera. When we learn that all tumors are composed of cellular units, subject to many of the laws governing the development and multiplication of cells in general, it is evident that this subject of shape as relates to lines of growth becomes an important study—one in which we are unfortunately quite ignorant.

Anyone who has handled tumors must have been impressed with the different grades of *consistency*. Some are so soft and friable as to fall apart on the most cautious manipulation; while others, even those not bony in nature, attain a stony density. Even in a single growth a uniform consistency is not always reached.

Most tumors are white, or show but a shade of grayish or pinkish color; but varieties are found which take distinct colors, like red, yellow, green, sometimes culminating in dead black. Usually the color of a tumor differs from that of its abode, so that its presence is readily detected. In exceptional cases a neoplasm so closely simulates the color and consistency of the structure in which it lies as to be discovered with difficulty.

In *relation to surroundings*, important differences, often highly important for the host, are met. A distinct membrane or *capsule*, a superficial covering of the tumor, separates it abruptly from the organ in which it is located, so that it can be enucleated with readiness. At other times the periphery of the tumor-mass remains sharply circumscribed, even though a true capsule is absent. Unfortunately, this respect for enveloping or contiguous structures is not shown by all kinds of neoplasms, since certain of them, without capsular boundaries, encroach more or less intimately upon the adjacent tissues until, in a particular class of tumors, an unbounded invasion occurs.

Upon incision and dissection, even without microscopic aid, a great deal may be learned concerning tumors. In many of them the resemblance to familiar animal tissues is so great that no trouble is experienced in recognizing their nature. Thus the fibrous, cartilaginous, and bony tumors, the fatty and the blood-vascular tumors can at once be placed in their proper categories. The tumor-tissue is generally quite uniform and homogeneous in appearance; but to this rule there are many exceptions, for heterogeneous material of a fatty, cheesy, gelatinous, or purulent appearance is present in some tumors, along with fluid contents like blood, urine, bile, and serum. Again, it is possible to obtain from a single tumor portions of distinctly different structures, like islands of cartilage or bone in a fibrous ground-substance. Such formations are called *mixed*, in contradistinction to the *simple* tumors.

The question of *habitat* is most tersely answered by Ziegler, when he

states that "tumors may be found in any tissue possessing capability of growth."

As to the *multiplicity of tumors*, all gradations from a single example of one variety to countless numbers of new growths in the same organ or tissue, or in different organs, are observed. Sometimes a number of similar growths may arise independently; or several distinct varieties of tumors, also of independent origin, may be simultaneously encountered in the body. In one portion of the body the original or *primary tumor* may be located, and scattered from it, both near and far, other neoplasms of the same nature (*secondary tumors*) are to be found. These secondary tumors may possess considerable bulk; they may be nodular growths; again, they may be scattered in dust-like particles, permeating a whole organ as a *diffuse growth*.

Histologic Features.—The study of the minute anatomy of tumors, especially when aided by improved histologic methods, has furnished most important additions to our knowledge; and as methods are refined, more and more is learned. A rational foundation was laid for the study of these objects when it was discovered that tumors, like the organs and tissues of the body generally, were composed of *cells* the morphology of which was often like that of one of the fundamental tissue-elements. It was this morphologic identity which led to the conviction that *tumors arose from cells which were pre-existent in the body*. Many attempts to shatter this conception of the origin of tumors have been made, but it must still be held inviolate; and with this notion clearly before us it becomes an easier task to interpret both their histologic and anatomic variations.

The cells composing many of these adventitious growths not only arise from pre-existing cells, but they retain many of the morphologic peculiarities of their parentage; they should therefore tend to reproduce the structural features of their prototypes. This is essentially the case, for these cells exhibit the structure of tissue-cells, and their grouping, their intercellular substance, their vascular supply, and even their metabolic products may all recall their ancestry. Thus the details relating to the cellular morphology of many kinds of neoplasms become but a rehearsal of the characteristics of normal tissue-elements. It is sufficient here to say that we find fibrous, fatty, cartilaginous, osseous, muscular, neural, and glandular tumors, the component elements of which resemble in structure and arrangement similar cells in normal tissue. Moreover, what holds true for the cells also applies to the elements of the cell—to the cell-wall, cytoplasm, and the nucleus with its component parts. These considerations, firmly fixed, make it clear that for most tumors there exists no such thing as a *specific tumor-cell*—a cell so peculiar in its organization that from it alone one could say that it sprang, not from normal tissue, nor from tissue the seat of inflammation, of infection, of regeneration, or of hyperplasia, but from a tumor. A fundamental point in relation to the microscopic anatomy of tumors is hereby emphasized, for it is not so much by their microscopic elements that these objects are differentiated, as by the *relation of these elements to each other, and especially to their environment*.

Tumors the elements of which exhibit the morphologic stamp of mature normal tissue generally have no strikingly peculiar physiologic characteristics, and are separately considered as *benign* or *benignant* neoplasms; their growth, like their structure, is orderly, and a respect for surrounding tissues

is shown. The attainment of morphologic perfection, such as has just been described, is not the case with all morbid new growths, for several varieties of tumors appear in the human body, the cellular units of which show a more or less marked deviation from typical mature tissue. Instead of reaching this perfection, the elements stop short in their development at one or another of the stages exhibited by immature or even by embryonic tissue. One species of these tumors (sarcoma) has, in some varieties, the cells, evidently predestined to become mature mesodermic tissue (connective tissue, endothelium, etc.), perverted and permanently arrested at a stage reached only by undeveloped mesodermic cells; while in another species (carcinoma) a predestination to mature ectodermic structures (epithelium, glands, etc.) seems to have been aborted. In these, the so-called *malignant tumors*, the component cells, both in their internal structure and in their groupings, depart more or less widely from the normal tissue-types, and there is a lawlessness in structure in their growth which shows no respect for environment. Not only do these neoplasms tend to disregard local confinement: they also possess the power of *colonization in remote parts of the body*. From a solitary tumor in a given locality new growths of the same kind may appear, either in the immediate vicinity of the original focus or scattered throughout the body. This process of colonization is usually designated *metastasis*; the offspring of the original colony *metastases*; and the "malignant tumors" practically monopolize this property. The departure from the normal morphology affects the whole cell with its component parts to such an extent as to make it possible occasionally to discover the presence of the tumor by the peculiarity of its isolated cells—principally by the nucleus and by the appearance presented by the figures of nuclear division.

Besides the proper tumor-cells, arranged in various combinations, there exists a *supporting ground-substance*, or *stroma*. In those neoplasms the structure of which takes the general type of pre-existing mesodermic tissues this stroma very closely resembles the connective-tissue framework of normal tissues, and forms an integral part of the growth, serving as a pathway for blood-vessels and lymph-vessels. In ectodermic (epithelial) tumors this framework or stroma is particularly prominent, sharply defining itself from the parenchyma proper. A striking peculiarity of certain primary malignant tumors is their ability to appropriate to themselves, as stroma, the framework of the organ in which they lie, in some cases even using the walls of capillaries as supports for their cells.

In and between the tumor-cells, or scattered through the stroma, *other microscopic elements* are found in tumors. Leukocytes, especially polymorphonuclear neutrophiles and lymphocytes, are present, sometimes in enormous numbers, both in the blood-vessels, in the tissue-spaces, and even within the tumor-cells. In tumors the seat of inflammatory reaction leukocytes accumulate in foci, or large abscesses may be found. Another variety of cell, probably originally a lymphocyte of the blood, is often found in the substance of tumors or in the immediate vicinity of the new growth, making a considerable bulk of the small-cell infiltration. These cells stain deeply with methylene-blue, and are doubtless identical with the so-called "plasma-cells" of Unna. Again, especially at the growing borders of tumors, both benign and malignant, cells with granules staining specifically with the basic dyes (safranin or gentian-violet, for

instance), and probably having their origin in connective tissue, are to be seen. Ehrlich and his pupils have designated these elements "mast-cells" (Mastzellen), though their significance is not yet clear. Acidophile granular cells, representing apparently both true and pseudo-eosinophile cells, also abound at times, especially where blood-destruction is going on. Connective-tissue cells in various stages of activity appear, often forming a large bulk of the small-cell infiltration marking the advance of certain growths. The cells composing some tumors seem to functionate much as similar normal animal cells do, and the microscope reveals many of the products of their metabolism, both in the tumor-cells and in their neighborhood.

Vascular channels for blood and lymph are found in neoplasms in varying proportions and degrees of perfection, and within the vessels the usual morphologic elements of blood and lymph are present. In certain rapidly growing tumors the development of blood-vessels may be so imperfect as to amount to little more than a channel between rows of tumor-cells.

An interesting question lately revived relates to the presence and source of *elastic tissue* in tumors. Where the tumor-stroma is formed from the framework of the parent tissue, elastic tissue exists as it originally did, apparently in an unaltered qualitative and quantitative condition. Whether new elastic fibers are formed in tumors manufacturing their own stroma is not positively determined, though the application of the recently perfected methods for their specific staining seems to render highly probable the view that certain tumors, both benign and malignant, ectodermic and mesodermic, are capable of elaborating new elastic tissue during their growth.

Another profitable inquiry refers to the presence of *nerves in tumors*. Eliminating those new growths arising from the central or peripheral nervous system, and naturally including nerve-cells and nerve-fibers, what can be said about the presence of vasomotor nerves in the blood-vessels of the stroma, or of sensory nerve-fibrils in the tumor-substance? All that can be asserted is, that nerve-fibrils are sometimes present in various kinds of neoplasms; but as to whether these elements represent simply the fibers previously present in the locality occupied by the foreign growth, or whether they are developed in the tumor from rudiments left in the mother-tissue, cannot be definitely answered at this time.

GENERAL PHYSIOLOGIC FEATURES.

Tumors are actual animate objects when encountered in the sites they naturally select in the living animal body. They exhibit the same evidences of vitality that enable us to judge of the life of any living animal, organ, or tissue. They grow, and, like other living things growing, they must receive nourishment, and receiving food necessitates a process of metabolism. They are supplied with nutritive juices, mostly through blood-vessels and lymph-vessels, in which course living elements, all provided by their host. They are subject to incidental diseases like the general tissue of the body. In short, these growths of new tissue which exhibit so many morphologic resemblances to normal animal structures live under many of the same physiologic laws that govern living things generally; and, like the organs of the proper animal body, they cannot live independently of their possessor. Severed from their organic connections they die, just as an amputated

limb dies; and there is little positive evidence that, when artificially reimplanted in the body of the host, or of another animal, they can again grow, or, if at all, but temporarily and imperfectly. With the assurance that tumors themselves and their cellular components respond to general physiologic laws, it will here be unnecessary to pass in review all the details of their life history. Rather let us turn our attention to certain features of peculiar interest—some of which might be styled the *morbid physiologic characteristics of tumor-elements*.

Morbid Physiologic Processes in Tumors.—Tumors are composed of cells, and since we know from observation that tumors grow, it follows that, like other living animal structures, they grow by division of their component cells. In tumors most closely simulating tissue-types, and generally of benign tendency, *cellular reproduction* is an orderly process, with the usual phenomena of nuclear and cellular division seen in normal animal cells. The operation of nuclear division occurs both by the method of direct and of indirect segmentation (karyokinesis). In the tumor-cells themselves karyokinesis is the most constant method of nuclear division, and, so far as our present means of observation go, this phenomenon proceeds generally in an entirely normal manner.

A general tendency, which often prompts them to grow with extraordinary rapidity, and to force their way through surrounding structures, and to break through confining cavities, which is especially the attribute of sarcoma and carcinoma, is very frequently reflected in the reproduction of their cells. The nucleus, in its division, may exhibit such departures from the normal method as to make appropriate Hansemann's term of "pathologic mitosis." In sections of such tumors, appropriately stained, one may find cells with small shrunken nuclei, containing but little chromatin, or sometimes in the same tumor monster cells with gigantic single nuclei, rich in chromatin. The number of chromosomes may be small (hypochromatosis), or much in excess of the normal (hyperchromatosis). Karyokinesis, or mitosis, may proceed by many peculiar irregularities. A marked disproportion in the two masses of chromatin, resulting from the unequal disposition of the chromosomes, gives rise to an "asymmetric mitosis." Even more striking is the phenomenon of "pluripolar mitosis," in which, instead of two attraction-spheres with their centrosomes at the poles of the dividing cell, from three to twenty or more attraction-spheres and centrosomes may be discovered in a single cell, disposed about the large and irregular central mass of chromosomes. Not infrequently, besides these cells with pluripolar mitosis, large multinuclear cells (giant cells) are found, doubtless representing a stage in the division of the pluripolar cell. Giant cells also originate from indirect nuclear fragmentation, which reaches a high degree of development in certain malignant tumors; and in this class of tumors karyokinesis is often replaced by direct segmentation or fragmentation. It must not be concluded, however, because these various irregularities in cellular reproduction (with the possible exception of asymmetric mitosis) are frequently found in malignant tumors, that they are peculiar to them. They certainly are pathologic occurrences; but they may develop in other situations—*e. g.*, in segmenting ova under injurious conditions, or in mature animal tissues under the influence of certain toxic agents or other pathologic factors. Besides those processes which indicate an abnormal cytologic reproduction are others that can only be regarded as degenerate in

tendency, indicative of impending or actual death of the affected cells. The chromatin of the nucleus gathers in irregular masses, which break into fine, dust-like particles (karyoclasia). These fragments or dust-like particles of chromatin may disappear by solution (karyolysis). Within the nucleus, or in the cytoplasm, bodies of various kinds and shapes ("cell inclusions") are not infrequently found. These bodies vary widely in their nature, being composed of escaped chromatin, of included and degenerated leukocytes or red blood-cells, of cellular or nuclear material with hyaline or other similar metamorphosis. The process of *vacuolation* is also seen in tumor-cells, especially of carcinoma, and immense cells with numerous dropsical cavities have been described. These changes, and others to be described, show that tumors are subject to degenerations, often culminating in death of the affected part.

Tumors situated upon the exterior of the body not uncommonly exhibit *necrosis* or death of their superficial portions, evident in more or less extensive *ulceration*. This destructive tendency is not confined to external neoplasms alone, for those situated within the body are also subject to its ravages. In some tumors large areas become necrotic, and microscopic examination shows a *diffuse necrosis* of the cellular elements. Besides these diffuse necroses there may be a process of *focal* or *insular necrosis* affecting the whole new growth, or confined to certain portions of it. This focal necrosis of tumors has many of the histologic features of focal necrosis in general, and resembles very closely this phenomenon when resulting from the action of various toxic agents, like ricin, abrin, snake-venom, or the poisonous products of bacteria.

Along with the degenerative changes culminating in the death of tumor-cells, a marked activity of the leukocytes and endothelial cells engaged in the operation of *phagocytosis* is frequently seen. The white blood-cells and the cells from the fixed tissues (lymphadenoid organs, the perivascular lymph-sheaths, or the connective-tissue lymph-spaces) gather about the dead and dying cells, both between and within them, and proceed to take into their substance such detritus as dispersed chromatin and nuclear or cellular débris. Occasionally the leukocytes, themselves in a condition of seeming degeneration, appear in the substance of apparently healthy tumor-cells, and it is a delicate question at times to decide whether the leukocytes were feeding on the cells or the cells upon the leukocytes. As a matter of fact, it is highly probable that both processes occasionally occur. Giant cells also arise in certain tumors in response to a phagocytic impulse, notably those appearing about the cholesterol crystals resulting from peculiar retrogressive changes (*cholesterin giant cells*).

The very close resemblance between the inflammatory and degenerative changes in tumors and those seen in other tissues the seat of infection suggests the possibility of the *infection of tumors*. That such an event actually takes place in tumors is shown by the frequent presence of micro-organisms. At least three kinds of vegetable parasitic organisms have been found in tumors, viz., the schizomycetes, or bacteria; the blastomycetes, or yeast fungi; and the hyphomycetes, or moulds. The presence of parasitic protozoa has also been urged by many observers.

It was the discovery of bacteria in certain neoplasms that first led to the promulgation of the parasitic theory of their origin, although more careful study showed the fallacy of the assumption in the cases in which it was advanced. In their turn the bacterial protozoa, the blastomycetes, and the

hyphomycetes have been held responsible as causative agents, as will be noticed under the head of Etiology. Whatever view may be held as to their etiologic relations, it is certain that many of these organisms invade tumors after they are formed, just as they invade other portions of the living body; and the gateways by which they obtain access are the blood-channels and lymph-channels when from remote regions, or directly when the tumor lies contiguous to an infected area or comes in contact with the exterior of the body. In the skin and mucous membranes, which constantly harbor micro-organisms, invasion is an easy matter.

Both saprophytic and parasitic bacteria may find their way into tumors, and the effects produced by them largely depend upon their pathogenic activity. These new growths are composed of masses of living cells with various kinds of intercellular substances, much like normal tissue, and from this structural condition it is to be expected that bacteria will inflict much the same damage as in the body at large. That such is the case is proved, for instance, by the production in tumors of inflammation, of pus, and of abscesses by the pyogenic bacteria. The vast number of leukocytes attracted to certain tumors is doubtless often a reaction produced by the toxic products of a bacterial infection; and the diffuse necrosis, or the localized (focal) necrosis, especially seen in tumors situated so as to invite invasion, is in all probability frequently the outcome of micro-organismal activity. This secondary invasion of micro-organisms is not always a harmful process, for there is undoubted evidence that certain infections have the power to cause arrest or even retrogression of some neoplasms, though this much-desired outcome is generally only a temporary one. Artificial infection of tumors with living bacteria, or the introduction of their toxic products, also appears to have a similar effect.

From many of their analogies, tumors may be compared to parasites living upon and at the expense of the host. It will therefore be profitable to consider here the *general relations of tumors to the host*. Many, with slow, orderly growth, are not harmful, or are harmful merely on account of their mechanic inconvenience. These are pre-eminently the *benign tumors*. Others of this class may be injurious because they act as foreign bodies. Thus, an immense abdominal tumor may become an actual burden by its size; and benign growths in the eye, ear, the central nervous system, or at the duct of some important organ may work serious mischief, even in their natural state of innocence. The case is entirely different, however, with the *malignant tumors*, which are, from their very inception, vicious in tendency. They generally grow rapidly, and even in their primary abode are not restrained, but proceed to spread in various directions. Their cells penetrate the natural spaces or clefts in the parent organ or tissue, and may even melt away more solid obstacles, like bone, which may perchance lie in their way. When this unchecked growth takes place in an important organ it is overrun and sometimes completely destroyed, the place of its own elements being taken by the foreign mass. This process affecting a vital organ, death of the individual is the natural and inevitable consequence. In their power of metastasis, also, the malignant tumors work great damage. Through the blood-vessels and the lymphatics, or by transportation over contiguous surfaces, the cells of the parent tumor are carried, and, lodging in another locality, their capacity for multiplication unimpaired, they produce secondary growths quite like those from which they sprang. Not

uncommonly the parent neoplasm is situated in a neighborhood in which it works no great mischief; but its offspring, locating in remote and often vital organs, lead to destruction.

With their propensity to become infected with pathogenic and especially pyogenic bacteria, tumors sometimes indirectly inflict damage upon the patient. The toxic products of this pyogenic infection in the circulation produce a general toxemia, which is shown by such phenomena as fever, chills, and progressive debility. It is also highly probable that in their growth the malignant tumors sometimes elaborate toxic agents through the perverted metabolism of their cells, these products again working harm to the host. The *cachexia*, or peculiar debilitated condition of individuals afflicted with malignant tumors, doubtless originates at times from this kind of slow poisoning.

THE ETIOLOGY OF TUMORS IN GENERAL.

There never has been a time when the subject of the causation of tumors needed so cautious an approach as now. With the vast mass of literature now available upon tumors in their various aspects, it becomes a difficult task to isolate the fundamental facts, particularly for purposes of didactic presentation; and nowhere is this difficulty more keenly felt than in connection with the question of etiology. Probably in this, as in other cases, a particularly unsettled state of affairs presages the birth of something new, and perhaps we are now on the eve of another era in our knowledge of tumors. Still, this important subject cannot be ignored in a treatise of this character, and brief reference to some of the views will therefore be made.

Mechanic irritation, traumatism, and previous local infection predispose to the development of tumors, and will be treated of in connection with special neoplasms. They must be regarded only as factors, however, and further search must be made for the real causative agency.

Granting that all tumors in the human body have their inception in pre-existent cells, we still have for consideration the problem which inquires into the causes leading to their development from these tissue-elements. What agency initiates the cells in this or that locality to such unusual activity as to produce from a cell, or a group of cells, by their proliferation, the tumor-mass? Why should this proliferation differ in its results from that seen in tissue regeneration, in hyperplasia, or in the new growths resulting from certain infections?

In 1882 Cohnheim attempted to answer these questions by propounding his *embryonal theory* of the origin of tumors. In its essence, as modified by its author, Cohnheim's theory ascribes the inception of tumors to misplaced embryonic rudiments, cells or aggregations of cells, which, during the various and complicated foldings of the embryo, and the shifting of its cells, become misplaced. In the further development of the embryo these tissue-rudiments are supposed to lie dormant but alive, and at some subsequent period, either early or late in the history of the individual, they resume activity and furnish the nucleus from which, by cellular proliferation, a tumor arises. This theory, though of purely speculative origin, has much to lend it support. Indeed, for a certain class of neoplasms—those arising in the fetal period or those distinctly congenital in their origin, or

that class containing more or less perfect reproductions of various kinds of mature tissues, and even organs of the body (the *teratoma*)—Cohnheim's hypothesis seems to afford the only rational explanation. It also furnishes the only satisfactory explanation of the genesis of many of the so-called benign tumors. One great drawback to the acceptance of the embryonic theory has been the difficulty of scientific demonstration, both of the actual presence of the misplaced rudiments, and of the production of tumors by artificially establishing the conditions assumed as requisite. The possibility of the misplacement of embryonic cells seems, however, to have been demonstrated, and it is even known that such cells may retain their vitality through a considerable period of time. It has also been shown by competent observers that islands of cells (rudiments of tissues or of organs) may be found outside of their normal habitat in adult animals; *e. g.*, cartilage and bone in the tonsils, cartilage in the kidneys, epithelial structures in the uterine parenchyma, and the frequent presence of "rests" of such organs as the adrenals, thymus, and thyroid. With these facts in mind, it becomes quite reconcilable that the genesis of tumors tending to reproduce mature tissue-elements, and of those arising from rests of misplaced organs, should be explained by Cohnheim's theory. The great problem, however, that still remains, granting the possible existence of misplaced rudiments, is, What factor stimulates these aberrant cells or cell-colonies to produce a neoplasm? It is just here that speculation has been especially active. In this connection Ribbert's ingenious hypothesis may be mentioned. He holds that tumors arise both before and after birth from a partial or complete separation of cells or groups of cells from their organic continuity. Released from the influence of inclusion in the cell association these separated fragments (germs), if capable of increase, grow independently into tumors; provided, of course, they get into favorable surroundings and nutritive conditions. Depending upon the size and organization of the fragments the tumors may correspond in their main features with the parent organ, or they may differ from it in part or entirely. In the main, Ribbert attributes the genesis of tumors to mechanical isolation, the inherent properties of the isolated cells remaining unchanged during their proliferation. Here he is opposed by Hansemann, who maintains that a change in the nature of the cell ("anaplasia") must precede its response to proliferative stimulus if it is to become a tumor and not merely take part in a simple hyperplasia.

But whatever may be said as to the bearings of the embryonic theory in relation to tumors in general, it certainly is apparent that even its warmest adherents do not urge it as fully explaining the origin of malignant neoplasms. The latter have so many distinctive characteristics, and their analogies with some of the growths arising from infection are so numerous, that a *parasitic theory* has been advanced for their explanation. The finding of micro-organisms, like bacteria, yeast, and possibly moulds, in these tumors naturally strengthened this hypothesis. So far as the bacteria are concerned, it may be said that they are at present no longer considered as the etiologic factors. Many forms of cell inclusions which were interpreted as developmental stages of lowly animal parasites (*Protozoa*, or more specifically representatives of the class *Sporozoa*) have been considered in the last ten years as causative agents. At present the general tendency is to renounce the sporozoan theory, and to lay the weight of responsibility upon *Blasto-*

mycetes, or yeast fungi. Pathologists of the Italian school are especially prominent as advocates of the blastomycetic theory.

So far as the sporozoan theory is concerned, it has met with two serious obstacles to its acceptance—viz., the recognition that many of the cell inclusions looked upon as parasites are degenerated red and white blood-cells, hyaline masses, vacuoles, outcast chromatin, engulfed cells, and various kinds of artefacts; and again by the absolute failure of all attempts to cultivate these so-called organisms outside of the tumor in which they were found, or to induce their multiplication in inoculated animals. In these respects the investigators working upon the blastomycetic hypothesis have been more fortunate, for they have not only successfully demonstrated the presence of yeast or budding fungi in microscopic sections of some tumors, but they have accomplished the cultivation of these fungi upon artificial media outside of the body. The vital link in the chain of etiologic evidence is still lacking in establishing the possible relationship of certain species of blastomycetes to tumor production; that is, the experimental reproductions of true tumors by the inoculation of pure cultures into animals. Several of these blastomycetic species have been shown to possess distinct pathogenic activities, producing in experimental animals nodules which macroscopically resemble true tumors; but on histologic examination these nodules prove to be mere granulation-tissue growths, such as are produced by inflammatory reactions to several kinds of infection. Up to the date of this writing, no satisfactory evidence has been adduced to show that anyone has successfully reproduced a tumor with all the morphologic features of spontaneous true tumors by inoculation with pure cultures of yeast organisms obtained from an original tumor. To say, however, that this demonstration is not to be finally accomplished would be unwise; and to assert positively that several of the varieties of tumors may not originate from infection with different species of parasitic micro-organisms is scarcely a justifiable attitude.

Another theory for the origin of tumors, of which only a hint is now heard, is what might be styled the *autotoxic hypothesis*, which assumes that the products of perverted metabolism in animal organs or tissues produce morbid effects in the individual's own body. This theory has been accepted as accounting for several obscure morbid processes, and it will not be surprising to find it prominently espoused in connection with the etiology of tumors; nor is it beyond the bounds of probability, from what we already know of the effects of certain substances originating in the animal economy, that in one or more varieties of tumor they may play an important part. As suggestive analogies, we have but to recall the often localized myxedematous deposits in hypothyroidism, the localized increase of elastic tissue in scleroderma, and the irregular overgrowth of bone in acromegaly.

THE SPECIAL VARIETIES OF TUMORS.

THE SO-CALLED BENIGN TUMORS.

Fibroma.—Both in their gross and microscopic appearance the neoplasms classed as fibromas have a close resemblance to connective tissue. They form more or less circumscribed masses, usually readily demarcated from the surrounding structures. While generally roughly spheric in shape, particularly when found in the substance of a soft organ, they may assume various forms. Growing from free surfaces, they tend to take a nodular shape, producing some of the so-called papillomatous growths; these papillomatous fibromas of the mucous surfaces are represented by certain polypi, seen in the nose, for instance; and on the cutaneous surface they produce warty growths. The diffuse thickening of the subepidermal connective tissue characterizing elephantiasis is regarded as a fibromatous metamorphosis; so also is the increase of connective tissue about the peripheral nerves producing the growths known as neurofibromas, which take various shapes, like the round or knob-like amputation-neuroma upon the ends of severed peripheral nerves, or the net-like series of nodular tendrils seen in the *cirroid* or plexiform neuroma (Rankenneurom).

As a rule, the fibromatous tumors are of exceedingly firm consistency, giving at once the impression of their fibrous character. But some of the neoplasms classed with the fibromas are very soft, as the molluscum fibrosum, or very friable, as the mucous polypi.

On macroscopic sections the firmer tumors present a white, glistening surface, in which the coarse fibrous bands can often be traced; in the softer kinds the section is more homogeneous, and fails to show the fibrous bands. Even in a single tumor the section may not always be uniform, since harder and softer areas, and cavities filled with gelatinous or fluid contents, sometimes are found.

As its habitat a fibroma may select any region of the body in which connective tissue abounds, although a predilection is shown for such localities as the skin, periosteum, fascia, uterus, and mammary gland.

The tumors of this variety are generally encountered singly; but they may be multiple. Among the subvarieties, like neurofibroma and molluscum fibrosum, a tendency to multiplicity is the rule, and hundreds of nodules may be scattered over the body, usually in the subcutaneous tissue.

In its minute anatomy a fibroma exhibits the structure of connective tissue, and, like the normal tissue, varies chiefly in accordance with its richness in cellular elements. In the denser tumors the cells are relatively few, and their nuclei are compressed laterally, making long, narrow bands with compact chromatin, which lie in the midst of well-developed fibers, appearing like those of mature normal fibrous tissue. The blood-vessels are relatively few, and the lymph-spaces narrow, explaining the white, dense, and dry appearance of these masses on section. Subvarieties with greater richness in cells, in blood-vessels and lymphatics are met; in the softer kinds, an appearance much like embryonic or newly forming connective tissue is at times produced. Here the nuclei are quite large, round, or oval; and the chromatin is present as a well-marked reticulum, in which one or more nucleoli appear. A distinct cellular protoplasm is to be defined in most fibromas; but in some of the harder kinds, especially those of keloid, in

which the structure resembles a coarse scar-tissue, the nuclei lie along the heavy fibrous bands making the bulk of the tumor-mass.

An important question relative to fibromas and other varieties of connective-tissue tumors is that concerning the development of elastic and collagenous substances in the groundwork. While some work has been done in this direction, particularly by Unna and his followers, the details as to the source of these tissue-components, their significance and fate, have not been accurately determined. According to Melnikow-Raswedenkow, tumors contain very little elastic tissue; no new formation of such tissue takes place in the substance of the tumor. But this view is not sustained, especially by recent studies of the American investigators—Alice Hamilton, Williams, and White—who find elastic fibers frequently present in tumors, either in the stroma, among the cells, around the blood-vessels, or around

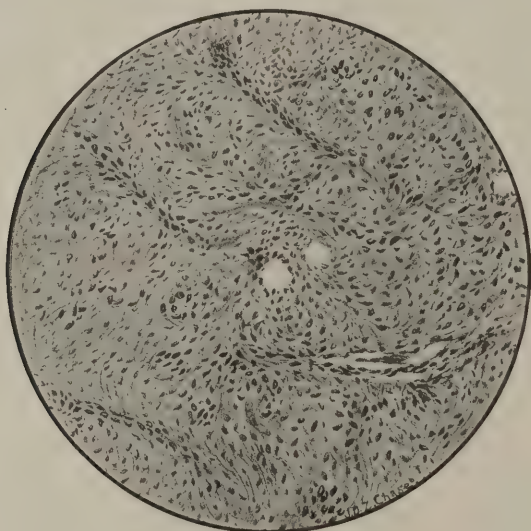


FIG. 53.—Soft fibroma. $\times 135$.

the milk-ducts in mammary neoplasms. This elastic tissue is usually in connection with the pre-existing elastic-tissue elements of the matrix, although new formation also probably occurs.

A richness in cells is not the only factor productive of soft fibromas; thus, in the mucous polypi the scanty cells with the delicate fibrils are widely separated by a deposit of mucin-containing material; and in other tumors serous fluid may accumulate in the substance, producing a softened, edematous condition.

The blood-vessels in fibromas, as a rule, show the ordinary histologic structure, but they may present distinct alterations, especially a thickening of the middle and external tunics, resulting in a narrowing of the lumen. Polymorphonuclear leukocytes and lymphoid cells are not numerous in fibromas unless inflammatory or degenerative changes are in progress, but mast-cells are often found in large numbers, particularly at the growing

borders of the tumor, and in those undergoing mucinous alterations. However, from the fact that these latter elements are found in several varieties of tumors, both benign and malignant, as well as in other pathologic tissues, it is hard to determine their significance unless, indeed, they be the forerunners of mucoid metamorphosis, as Harris has recently suggested on the ground of some very suggestive similarities in staining-reactions.

With the exception of the neurofibromas, nerves have not been demonstrated in this variety of neoplasm. In the case of the neurofibromas which may form in the cerebral, spinal, or sympathetic nerves or their ganglia, it is generally held that no new formation of nerve-fibers occurs. The tumor takes its origin either from the endoneurium of a peripheral nerve, pushing aside the nerve-fibers until they become widely separated, and even perish from pressure and disappear, or from the perineurium or epineurium, growing laterally from the original nerve-trunk, sometimes surrounding it without disrupting the natural arrangement of the nerve-fibers. It is therefore clear why a histologic study of the neurofibromas, as found in the skin and along the course of peripheral nerves, should show gradations relative to the nerve-fibers, which sometimes are abundant, again isolated or even absent, and why these fibers vary from apparently normal medullated fibers to naked axis-cylinders, or axis-cylinders variously deformed.

The rate of growth of fibromas is usually slow, although not invariably so. Those richest in cells with well-developed cytoplasm and nuclei grow most rapidly. It is rare to find nuclei in any of the stages of mitosis; and it is quite probable that even in the more rapidly growing forms the type of nuclear division is a direct segmentation or amitosis.

The pure fibromas have no capability of reproducing true metastatic growths, and in most instances a recurrence after thorough removal by operative measures is impossible. An exception to this rule is found in keloid, especially in the spontaneous variety, in which the tumor recurs after thorough and repeated attempts at removal.

Inflammatory reaction, although rare in fibromas, may follow infection with pyogenic bacteria. Various metamorphoses or degenerations to which connective tissue in general is predisposed, such as mucoid or myxomatous, fatty, and edematous, may take place in these tumors. In fibromas of uterine origin cysts are sometimes found, and a cystic condition is not uncommon in the tumors originating in the mammary gland.

That some fibromas owe their origin to traumatism as one, at least, of the inciting factors seems definitely established, and is exemplified by the fibromatous keloid which develops in scar-tissue after injury or operation. A predisposition of the skin to fibromatous overgrowth, especially in the form known as spontaneous keloid, seems especially pronounced in the victims of a syphilitic or leprous taint, and in the colored race. Fibromas are also encountered as congenital growths, and in some cases an hereditary predisposition seems to exist, particularly with reference to keloids and neurofibromas.

Lipoma.—There is no special difference in the structural characteristics of lipomas and ordinary adipose tissue. In gross appearance these tumors simply present the characters of a localized mass of fat, in no way different from the normal subcutaneous fat. The microscope reveals the same resemblance, and the fat contained in these neoplasms responds to the usual chemical reactions of this substance. It was these points of similarity

which led to the assumption that lipomas took their origin in pre-existing adipose tissue.

The size of lipomas is subject to variation, certain of the neoplasms, especially those in the kidney and liver, being barely recognizable without microscopic aid; while others, especially the pendulous tumors seen about the neck and shoulders, may become massive. They are generally rather soft and yielding. In most cases the contour is regular, the formation of accessory nodules not being so common as in other new growths. A rigid respect for surrounding structures is ordinarily shown, and usually a fibrous capsule sharply isolates the fatty tumor from the structure in which it grows.

The subcutaneous tissue, especially about the back, shoulders, axillæ, and groin, is the favorite seat of fatty tumors. The viscera—in particular the kidneys, rarely the brain—may be affected. The tumors appear both in fat and lean individuals, generally in adult life; although they are to be found in children, and even appear as congenital growths.

The majority are solitary. However, multiple lipomas reaching considerable numbers have been described. Another curious variation in the appearance of fatty tumors is a symmetric disposition of two or more masses in the body, as, for example, in both groins and both axillæ.

Lipomas grow slowly and produce no disturbance, except by pressure or by mechanic interference.

Inflammation following infection, even leading to abscess, is a possible, though not a common, occurrence in fatty tumors. The fat in certain portions may soften, and by liquefaction an oil-cyst may be produced. An overgrowth of fibrous tissue makes a firmer tumor, usually designated a fibrolipoma, and a mucoid metamorphosis may occur in portions of a fatty tumor, making a myxolipoma.

A peculiar form of fatty tumor, the nature of which is not well determined, is the *xanthoma*. The xanthomas are usually small yellowish tumors with fat-containing cells, and are either located in the eyelid, or as multiple disseminated growths beneath the skin, or even in the internal organs, as the trachea, pericardium, splenic capsule, or the liver. Whether they originate from pre-existing fat-cells, or from a transformation of endothelial cells of the lymph- or blood-channels, is not determined; some believe that they may arise from a local bacterial infection. One peculiar feature of the xanthomas is the presence of multinuclear giant cells. They are sometimes met with in diabetic persons, having apparently some relation to the disease, "*xanthoma diabeticorum*."

There is no doubt that some lipomas originate as the result of injury. This is seen in the tumors appearing on the hands of working-people, in the portions most exposed to traumatism. These tumors have also been found springing from scar-tissue. In the case of the symmetric lipomas particularly, a nervous (trophic) influence is supposed to play a part. The embryonic origin of this class of tumors seems clear in the case of their appearance in infants and young children; fatty or lipomatous tissue, moreover, makes a large bulk of many teratomas.

Chondroma.—Tumors having a macroscopic and microscopic resemblance to cartilage are designated as chondromas or enchondromas. These growths vary in size, the smaller masses being nearly spheric, while the larger are irregular, nodular, or lobulated. A capsule of fibrous tissue generally serves to bound the chondromas. The tumor presents a homogeneous,

cartilaginous aspect on section; the larger masses may contain softened foci, and even cystic cavities filled with gelatinous material.

In minute structure an appearance more or less resembling normal cartilage is presented. The cells may be encapsulated or free, and are spheric in shape in most cases, sometimes large and again small. Oval, spindle-shaped, and branching cells appear in some specimens. The cellular elements may be closely and evenly set, widely separated, or aggregated in groups of varying size. The ground-substance may be hyaline, like hyaline cartilage, or more or less reticulated, like fibrocartilage. Foci of beginning ossification or of mucoid or fatty metamorphosis are quite common. Even in the hyaline variety the cartilage is isolated into islands, surrounded by fibrous tissue, which carries the nutrient vessels.

Chondromas may appear in situations in which cartilage exists normally, as about the articulations and in the trachea; on the other hand, they not



FIG. 54.—Chondroma of the lung. $\times 35$.

uncommonly arise in localities in which cartilage naturally is absent, as in the substance of well-developed bones, in the parotid gland, the testicles, the mammae, and even, in rare instances, in the skin. Multiple chondromas occur especially on the hands.

The pure chondroma is a tumor of slow growth. Its influence upon surrounding structures is mainly a mechanic one. This rule is not without exception, for certain varieties, instead of growing symmetrically and ignoring the surrounding tissues, send islets of tumor-cells into the tissue-spaces, especially in connective tissue and muscle, even for some distance beyond the principal tumor-mass. Finally, in rare cases, tumor-elements may be transported by the vascular channels, probably through invasion of the vessel-walls, secondary growth or metastasis being set up in distant parts of the body. Even in chondromas the morphology of which seems identical with the ordinary benign forms this may happen. These malignant

cartilaginous tumors are not to be confused with the mixed forms, in which sarcomatous elements predominate (*chondrosarcoma*).

In the development of cartilaginous tumors in regions which normally contain cartilage, it is only necessary to conceive of their origin from the cells previously existing, though little is known of the forces by which the proliferation of such cells is brought about. In the case of tumors which appear in fully developed bone, Virchow's theory is generally adopted. He holds that in these cases islets of cartilage were misplaced in the post-embryonic development of the growing bone, generally through rachitic changes, and that from these islets cartilaginous tumors later arise. The foci situated in the spongy portion of the bones form true chondromas, those in the more compact portions cartilaginous-osseous tumors or chondro-osteomas, while in the dense bony tissue pure osseous tumors develop. To account for the appearance of chondromas in tissue which never contains cartilage normally, the theory of misplacement of embryonic rudiments offers the only acceptable explanation.

Aside from the mixed forms of cartilaginous tumors (osteochondroma, myxochondroma, lipochondroma) brought about by the metamorphosis of portions of the tumor itself, a very interesting neoplasm related to the true chondroma, at least so far as genesis is concerned, should be here noticed. This tumor, described by Virchow as *echondrosis physalifera*, or better designated as *chordoma*, apparently has its origin in abnormally persistent remnants of the embryonic notochord, or *chorda dorsalis*. The most common situation is beneath the dura of the clivus (*clivus Blumenbachii*) of the body of the sphenoid bone, or about the junction of the body of the sphenoid bone with the occipital. This region represents the anterior extremity of the notochord. These tumors may also appear in the bodies of the vertebra. They are generally small (cherry size), and show on microscopic examination a series of large vacuolated cells with poorly defined boundaries, sometimes closely packed, and again separated by a homogeneous, structureless substance. The histology of these tumors closely resembles that of the remains of the chorda found by an examination of the region of the clivus under normal conditions.

The chondromas of the testicle and of the parotid gland are nearly always associated with other forms of tumor-tissue; hence they are called mixed tumors. Reference will be made to them later.

Osteoma.—Osteomas are tumors composed of osseous or bony tissue, either hard and compact or soft and spongy. They are situated in various parts of the body, either in connection with pre-existing bone or independently of it. They vary in size, the harder variety, which is usually multiple, being small, while the spongy bony tumor often reaches a large size. The microscopic anatomy of these tumors is essentially identical with that of various normal types of bone. It is often difficult to draw a sharp line between the chondromas and tumors containing osseous tissue, since they often merge into each other.

The process of ossification in bony tumors proceeds in the same way as in developing bone. Many of the smaller tumors of ivory-like hardness remain stationary after attaining a certain size. Ossification proceeds as a metaplasia, as seen in the transformation of cartilage and cartilaginous tumors into osteomas; as a reversion to former functional activity, seen in the dura of the cranium and of the spinal canal, which resumes its periosteal

or bone-forming function; or finally these tumors may arise by proliferation of elements the origin of which is unknown.

Bony tumors occur in connection with the skeletal system in any part of the body, as subperiosteal growths in connection with the bone, making surface protuberances, or in the bone-substance proper, or within the bone-cavity. Bony tumors growing upon the surface of bones are designated as *exostoses*, and are ivory-like in density or softer and more spongy, or even partly cartilaginous in some cases. Many bony new formations are, strictly speaking, not true tumors, inasmuch as they are the direct result of irritation and inflammatory action. It is, however, difficult to draw the line between osteomas and such bony growths, which are often designated as *hyperostoses*. True bony tumors not rarely occur symmetrically.

Osseous tumors arise in connection with the teeth, either from the enamel, the dentine, the cement, the tooth-follicle, the fibrous tissue about the teeth, or from the tooth-structure as a whole. To these tumors the general term *odontoma* has been applied.

Pre-existing cartilage may furnish the nidus for the development of bony tumors. Osteomas also appear in various soft parts, like the tendons, fasciæ, muscles, and very rarely in the skin and the viscera.

The multiple osteomas of bones are related to multiple enchondromas, and it is possible that, like the latter, they originate from misplaced foci due to errors in the normal process of bone-formation, as seen in rickets. A strange occurrence is the production of metastatic bone-tumors from original non-osseous neoplasms of the adrenals, mammary gland, thyroid, and prostate.

Myxoma.—A variety of connective-tissue tumor closely related to the preceding forms, and scarcely worthy of a special classification, is the so-called myxoma, or mucoid tumor. A myxoma in the sense of a tumor composed purely of myxomatous or mucoid tissue is really not known, since all tumors of this class shade more or less into other forms of connective-tissue neoplasms, particularly into the fibromas.

The myxomas are soft, gelatinous, spheric or lobulated tumors, varying in size in different situations. They are generally sharply defined from the surrounding tissues, and when growing from free cutaneous or mucous surfaces are often pedunculated, forming one variety of the so-called polypi. On section a moist, shining surface is presented. Their consistency is not uniform, especially in the larger growths, since denser bands or isolated areas are present in the midst of the soft, jelly-like mass.

Microscopically the tumors are composed of spindle-shaped or star-shaped connective-tissue cells, separated by clear spaces which with ordinary reagents do not stain, but by treatment with special staining reagents having an affinity for mucin (*e. g.*, thionin) show more or less of this substance. The amount of this intercellular material varies, not only in different tumors, but also in different portions of the same tumor.

The softer polypi found in the nose and ear are myxomas. Tumors of this class are also found in the skin, bone-marrow, mammae, peripheral nerves, the brain and spinal cord, and occasionally in other viscera (the heart and kidneys). The *hydatidiform mole* is regarded as a myxoma of the chorionic villi.

A myxoma grows with moderate rapidity. It possesses no power of metastasis.

Except in the congenital type of these tumors, the structure of which is

quite similar to the gelatinous substance of the jelly of Wharton in the umbilical cord, the myxomas apparently owe their origin to an edematous metamorphosis of a connective-tissue tumor. From some circulatory disturbance, or in some cases from an abnormal thinness of the blood-vessels, a serous fluid transudes into the meshes of the tumor, pushing apart the cells. This fluid is very similar to that found in ordinary edema of subcutaneous tissues, and the microscopic appearance of a myxoma is much the same as that of edematous connective tissue. The presence of mucin in this serous transudate is a matter of dispute, certain observers holding that true mucin is absent both in ordinary edematous tissue and in the myxomas.

Taking the view that an edema underlies the development of myxoma, it is easy to reconcile the various mixed types of tumors in which myxomatous tissue is present. The softer forms of fibroma are on the border-line with a moderate edema, while a localized edema, more or less rich in mucin, gives

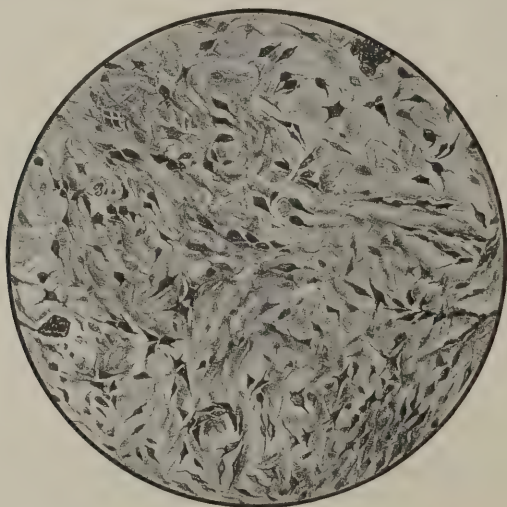


FIG. 55.—Myxoma. $\times 160$.

in lipoma, chondroma, osteoma, and occasionally in sarcoma, the mixed tumor-forms designated as myxolipoma, myxochondroma, myxo-osteoma, myxosarcoma.

Myoma.—Muscles, both of the striated and the unstriated variety, may constitute the principal component tissue in a class of tumors described as myoma. Those comparatively rare myomas composed of elements resembling striated muscle are called rhabdomyomas, to distinguish them from the more common variety with unstriated muscle-fibers, the liomyomas.

Rhabdomyoma.—In gross morphology there is nothing strikingly characteristic about the striped-muscle tumors, which vary considerably in size and shape, even forming polypoid masses when situated on free surfaces. While occurring in those localities in which striated muscle is normally present, the rhabdomyoma more often selects organs naturally devoid of striated muscle. The genito-urinary tract is a favorite seat for these striped-

muscle tumors (the kidneys in particular), more than half the recorded cases being confined to this system. Less frequently the cervical and orbital regions are involved, while the skeletal muscles, connective tissue, mediastinum, heart, and esophagus are still more rarely chosen. It is important to note that rhabdomyomas appear most commonly in early childhood, and that they have even been found in the newborn.

Two principal kinds of mesodermic tissue make the histologic basis of these morbid growths, a vascular connective-tissue framework, and an imperfectly developed striated muscle. The framework varies in amount in different tumors and in different portions of the same tumor, and it further varies in the richness of its cells and fibers, often complicating the structure of the tumor by its irregular behavior. A noteworthy point concerning the morphology of the myomatous tissue is that *it never attains the full development of mature striated muscle*, always stopping short of the production of perfect fibers with regularly disposed sarcoous segments. Indeed, the distinguishing histologic feature about these tumors is the immaturity of the component fibers, which strongly recall the various stages of developing or regenerating striated muscle-fiber never reaching completion. The fibers may attain considerable length and show quite regular and prominent transverse striae, or there may be both transverse and longitudinal markings. The nuclei may be flattened and disposed alongside the fiber in a manner somewhat recalling that seen in well-developed voluntary muscle. Other fibers are shorter, irregular in contour, often spindle-shaped, and show uneven transverse markings or none at all, while longitudinal lines may or may not traverse them. In these fibers the nuclei are often abundant, and sometimes large and vesicular, rich in chromatic substance, and disposed along the middle of the fibers. Finally, masses of sarcoplasm with chromatin-rich nuclei, entirely undifferentiated, are encountered. Probably the excess of these spindle, oval, and round cells in certain tumors led several observers into the error of considering them to be connective tissue or sarcomatous elements, resulting in the designation of these tumors as rhabdomyosarcoma. It is distinctly more appropriate to regard these cells as undifferentiated or embryonic muscle, since they correspond so perfectly to such cells seen under normal conditions of development or repair, although the occurrence of rhabdomyoma and sarcoma in combination is not to be denied. A further argument for the embryonal nature of these elements seems to be afforded by the frequent presence of glycogen droplets, both in the muscle-cells and the connective tissue. Islets of cartilage, of bone, of adipose tissue, and even of epithelial gland-like structures have been discovered in rhabdomyoma; and myomatous tissue such as has just been described is a not uncommon constituent of certain complex teratomas, especially those of the kidney and testicle.

As to the origin of the rhabdomyoma, it is now generally conceded that it is a neoplasm of embryonic aberration. Both the frequency of these tumors as congenital or infantile formations, their site in regions particularly involved in complicated embryonic foldings and shiftings, and the embryonal nature of their essential cells make this view a reasonable one. Recalling the part taken by the various rudiments in the formation of the kidney, it is not difficult to comprehend how a misplaced myotome or portion of a myotome could furnish the matrix from which a rhabdomyoma later developed; and with a participation of the sclerotome and nephrotome those more complex tumors with striated muscle, cartilage, and epithelial structures could

be explained. In the case of a rhabdomyoma of the myocardium, it has been shown that the tumor-elements reproduce, in their form and arrangement, the histologic picture of the heart-muscle of a four weeks' human embryo.

Liomyoma.—The type of this neoplasm is the familiar growth commonly and erroneously called "uterine fibroid." Some of these tumors are of enormous size, while others are minute. Both single and multiple liomyomas are found. The large uterine tumors are not infrequently nodular, while those found in the intestine may have a polypoid shape. The tumors are generally firm, white or pinkish in color, and glistening on section, in which close inspection will reveal the component fibrous strands travelling in different directions. It may show a cystic metamorphosis (*cystomyoma*), or the fibrous connective tissue may predominate, producing a hard tumor called a fibromyoma. By far the greater number of tumors of this class are found in the uterine musculature, especially after the onset of puberty. It is very rare to find them in the uterus of children, and they seem to be unknown as congenital formations. The alimentary tract is also a favorable location; occasionally they are found in the urinary bladder, urethra, and the larynx. In the skin, where they are at times met with, their origin seems to have been traced to the erector muscles of the hair-bulbs.

Smooth, spindle-shaped, nucleated muscle-fibers aggregated into narrow bundles and running in various directions in a more or less abundant connective-tissue stroma make up the essential histologic structure of these tumors. Maceration in 20 per cent. nitric-acid solution produces dissociation of the myomatous elements and permits their study as individual cells or cell-groups; but for tracing the muscular strands and for finer study, thin, well-stained sections are requisite. A point worthy of attention relates to the presence of blood-vessels in the center of these muscular bundles, especially to be seen in the smaller uterine nodules, and the interweaving muscular strands frequently pursue the same tortuous course as the vessels. This discovery has led to the conclusion that many of the liomyomas have their primary origin in the proliferation of the unstriped cells of the arterial muscularis; and certainly this view seems to fit most uterine myomas, and seems also applicable to those of the gastro-intestinal canal and to those dermal myomas which cannot be traced to the erector muscles.

The simple histologic structure of the muscle-fibers and connective tissue is sometimes complicated, especially in the tumors originating in the uterus, by epithelial cells in groups, in imperfect tubules, or lining cystic cavities. Their histogenesis is not fully determined, and they have in turn been ascribed to aberrant remnants of Gärtner's duct, Müller's duct, and of the Wolffian bodies. It is more likely, however, that the epithelial elements are derived from severed portions of the uterine mucous glands, which sometimes penetrate beyond the normal confines. In one case of myoma of the stomach, remnants of misplaced pancreatic tissue were recognized.

Many of these new growths contain mastzellen in abundance, sometimes in the proper muscular tissue and again in the tissues bordering the tumor. The significance of these peculiar granular cells in connection with liomyoma is entirely a matter of conjecture.

Obscurity surrounds the question of *etiology*. Transposition of embryonic rudiments may account for certain of the liomyomas, but not for all. In one case it was thought a diabetic dyscrasia provoked the appearance of

multiple dermal myomas; and the possibility of syphilitic influence has also been suggested.

Lymphoma.—The lymphadenoid tissue of the human body reacts to a variety of physiologic and pathologic impressions resulting in a proliferation of lymphoid cells which remain localized in the gland in focal accumulations, producing lymphadenoid hyperplasia and hypertrophy, gain access to the circulation, appearing in the blood as a lymphoid leukocytosis, or produce both lymphatic enlargements and lymphocytosis. Of the morbid influences leading to regional or general lymphadenoid overgrowth (with or without lymphocytosis) a number may be cited, as, for example, various acute and chronic infections, and the hematic dyscrasias designated leukemia and pseudoleukemia. In some of the latter class of cases lymphatic tumors, or lymphomas, may be produced, sometimes localized, again general. Enormous single lymphomatous tumors may appear, like those seen in the mediastinum, accompanied by multiple enlarged lymph-glands and the overgrowth of lymphoid cells in viscera like the kidneys. Such occurrences are often called "malignant" lymphoma, or lymphosarcoma, and the clinical and anatomic picture is enough like that exhibited by other malignant tumors to justify the appellation. However, these neoplasms are regarded as in some way induced by a perversion of the blood-forming organs, probably incited by an infectious or a toxic agency, and are therefore to be excluded from tumors proper. A clear distinction between the various pathologic conditions of the lymphatic system comprehended under the terms lymphoma, malignant lymphoma, leukemic lymphoma, aleukemic lymphoma, and lymphosarcoma cannot now be drawn.

Whether there is such a thing as a true lymphoma, a growth originating from and composed of the proper lymphoid cells, and imperfectly reproducing lymphatic structure independent of a localized or general infection, or of a disease of the hematopoietic system, is very doubtful. Such a tumor is described by some authors, but without sufficiently sharp distinctions. In other cases, especially with the solitary benign lymphomas which show enlarged lymph-nodes, the possibility of an infectious origin has not been ruled out. But it may here be appropriate to remark that we cannot be too critical regarding this type of neoplasm, for if we are to eliminate those tumors in which an infectious cause is suspected, and retain as true tumors only those in which an embryonic or non-infectious postnatal causal influence can be proved, then lymphoma, as just described, will appear in a goodly company.

Angioma.—Tumors composed of vascular elements in preponderance are designated as angiomas, and those of blood-vascular origin are usually separated as hemangiomas from those of lymph-vascular origin, which are called lymphangiomas.

Hemangioma.—Several varieties of blood-vascular new growths are encountered, and in some of them it is not clear whether the tumor really results from a new formation of blood-vessels or from a dilatation or hypertrophy of blood-vessels originally present. The diffuse reddish or purplish and slightly raised tumors often present as birthmarks and characterized as *nevi* or *telangiectasia*, belong to the doubtful formations, as they have in some instances been shown to be due to locally dilated capillaries. Another variety of these tumors is composed of communicating spaces filled with blood and bounded by partitions of purely connective-tissue origin; these

are the *cavernous angiomas*. But besides these doubtful forms, hemangioma occurs as a true tumor composed in bulk of newly formed blood-vessels, and these vessels may originate from the arterial, venous, or capillary system. One form of arterial angioma, from the thickened and tortuous development of its vessels, is known as a *cirsoid aneurysm* or *plexiform angioma*.

Hemangiomas appear as diffuse (often widespread) growths, or in circumscribed nodules, either beneath the surface or projecting from it. On account of the contained blood they usually can be readily recognized by their red color, and in the tumors projecting from a free surface, *e. g.*, the scalp, a tendency to free hemorrhage after even slight traumatism is characteristic. A distinct pulsatile expansion is sometimes noted, particularly in the nodular forms.

The microscopic anatomy of the hemangiomas varies according to the



FIG. 56.—Cavernous angioma of the liver. $\times 135$.

nature of the new growth. In the tumors with venous or arterial vessels their structure is quite similar to those vessels found normally in the body. In the nevi the vascular channels have somewhat the structure of capillaries, with a thickening of the walls and dilatation of the vessels. Groups of these vessels, surrounded by connective-tissue septa, are found beneath the skin, covered superficially by intact epidermis, and appearing in situations normally occupied by fat lobules. Here and there, in the midst of the group of vessels, hair-follicles, sweat- and sebaceous glands can be seen. The vessels composing these groups have endothelial walls, usually several cells deep, and surrounded by a poorly defined basement-membrane. That active proliferation is going on in some, at least, of this variety of angioma is evident from the presence of karyokinetic figures in the cells of the vessel-wall.

The *nodular angiomas*, usually projecting above the skin, show a very irregular development of blood-vessels. Sometimes they appear as capillaries with greatly thickened walls, with little intervening tissue; again the walls are thin and composed of little more than a single layer of endothelial cells. Finally, the vessels may be considerably dilated (often irregularly), and partake of the nature of poorly formed venous channels.

In the *cavernous angiomas* the masses of blood, varying greatly in size, appear in spaces bounded by thin walls which exhibit the structure of connective tissue and are lined with endothelial cells. The peculiarity of the vascular structure seen in the walls of these cavities has led Ziegler to regard these formations as separated from true tumors. In a multiple cavernous angioma of the liver he was able to trace the original tumor to the dilatation of a single capillary, and to consider the resulting growths as due to a cavernous metamorphosis of the liver-lobules. Besides the blood-elements in normal proportions, an excess of leukocytes can be found in some of the cavernoma, and a deposition of fibrin-threads and the formation of thrombi may be encountered. Either from their escape into surrounding tissues (hemorrhage) or from stagnation in the angiomatous spaces, the blood-cells may perish and remain as foreign bodies, calling into play the process of phagocytosis in their removal. Leukocytes and the offspring of the fixed tissue-cells appear in and about the angioma, loaded with blood-corpuscles in various stages of disintegration or with hematogenous pigment. Occasionally these scavenger cells become so numerous as to give the tissue an aspect suspicious of a sarcomatous or melanosarcomatous growth, seriously complicating the histologic picture. It is almost superfluous to add that a similar phenomenon is seen in other varieties of tumors in the event of hemorrhage or death of red blood-cells.

The diffuse angiomas, or teleangiectases, are usually found in the skin, especially of the head and neck, and for the most part are congenital in origin or appear shortly after birth. Some of these formations occur at points at which clefts unite during fetal life, and they are therefore designated fissural angiomas. Diffuse hemangiomas are occasionally met in the muscles, the breast, and the viscera. The skin is also the seat of the majority of the nodular angiomas, and a tendency to multiplicity is by no means uncommon. A particular kind of multiple nodular hemangioma of the skin is found in old people—the so-called senile angioma. Cavernous angioma may also appear in the skin; but it is more often located in the viscera, especially the liver. Both the nodular and the cavernous hemangiomas have been found in various organs of the body, including the central nervous system, and even in the bones.

As to the etiologic factors concerned in the formation of these tumors, we must admit that developmental or embryonic influences play a prominent part in many of the diffuse congenital neoplasms of childhood. Traumatism is also an important agent in favoring the development of certain hemangiomas, and such factors as variation in the blood-pressure and the velocity of the blood-flow and obstructive agencies must, as Thoma has pointed out, take a prominent part. The cavernous angiomas of the liver are usually well circumscribed by a fibrous capsule; this, among other features, has led Ribbert to look upon them as due to the development of preformed congenital structures.

Lymphangioma.—As is the case with the blood-vascular tumors, so the lymphangiomas are doubtless of two kinds—viz., true tumors in which new growth of lymph-vessels takes place, and tumors arising from dilatation of pre-existing lymph-channels or from their hypertrophy; and, like the hemangiomas, we find subvarieties of the lymph-vascular neoplasms depending upon morphologic peculiarities. Thus there is a diffuse new formation of lymph-vessels, or a widespread dilatation of pre-existing vessels producing a *lymphatic teleangiectasis*, and another form with irregular spaces, making a *cavernous lymphangioma*. In still another form distinct cysts are present—*cystic lymphangioma*; and sometimes these cysts contain chyle—*chylangioma*.

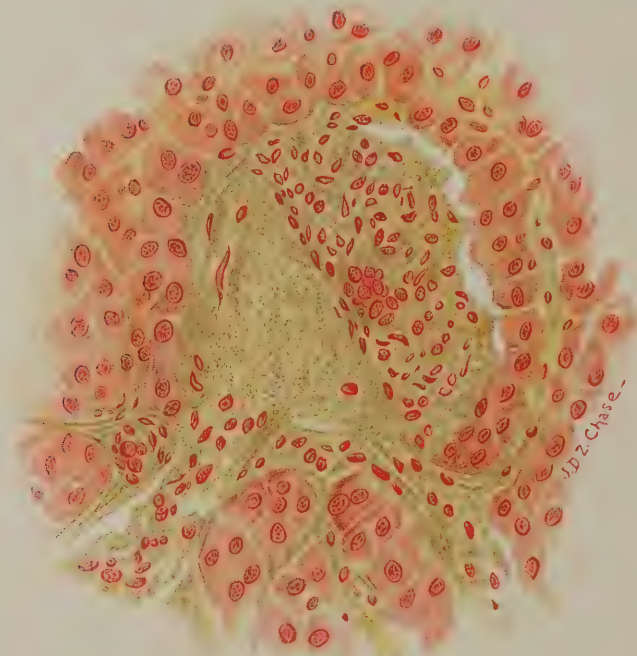


FIG. 57.—Lymphangioma of the liver. $\times 500$.

A diffuse lymphangiomatosis, when present in the tongue, is technically styled macroglossia, in the lip macrocheilia, beneath the skin of the neck hygroma; and in the skin this formation is known as a lymphatic nevus. Sometimes the cutaneous lymphatic nevi are pigmented. A local dilatation or hyperplasia of lymph-vessels more or less diffuse is the essential pathologic condition in certain well-known pigmented birth-marks; and to the same category freckles and certain cutaneous warts belong.

Both the diffuse and circumscribed lymphangiomas may attain considerable size, and in the cystic and cavernous varieties the tumors are often multiple. The contents of the tumor may be clear lymph; or this fluid may be

cloudy, and contain lymph-corpuscles, or even blood-elements. Sometimes the fluid is partially or completely coagulated or solidified.

Histologically these tumors are characterized by their resemblance to lymph-vessels or lymph-spaces found in healthy tissue. A series of communicating clefts or spaces abound, which are lined with endothelium and surrounded by a more or less perfect framework of connective tissue, which is usually well supplied with cells. Scattered through the connective tissue islands of small round cells (lymphocytes) often abound.

The favorite seat of this variety of neoplasm is in the skin or subcutaneous tissue. They are more rarely found in connection with the digestive tract, and very rarely in the peritoneum and viscera.

Many of the lymphangiomas are congenital in their origin, as seen in

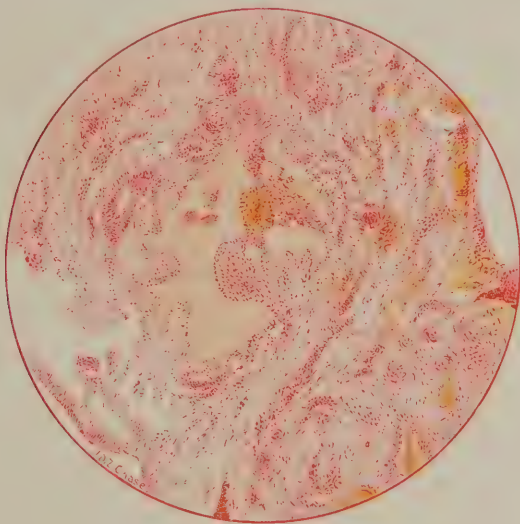


FIG. 58.—Lymphangioma of the skin. $\times 35$.

macroglossia and in pigmented moles or birthmarks; and this observation also holds true for the cystic and cavernous varieties. It would also seem that developmental errors are responsible for the origin of these formations. The tumors of this class may also appear any time after birth, some instances of their development in old age having been noted. As has been remarked, some of these formations must be regarded as diffuse or localized dilatations of pre-existing lymph-channels, and here the important factors must be the obstruction or stagnation of the normal lymph-circulation. Thus the chylangiomas probably are cysts originating in some interference with the normal output of Lieberkühn's glands in the small intestine (Lubarsch). However, there can be no doubt that in many of the lymphangiomas, both in the congenital and acquired forms, an actual new formation of lymph-channels takes place, though by what agency we cannot say.

In both the pure hemangiomas and the lymphangiomas the growth is benign; but since these tumors are largely composed of newly formed endo-

thelial elements, they are brought into proximity with a variety of sarcoma (endothelioma) which is of a destructive nature; and the gradation from a simple blood-vascular or lymph-vascular neoplasm to one or another of the forms of endothelioma is sometimes encountered, and is difficult to recognize histologically.

The Fibro-epithelial Tumors.—This is a class of tumors with two chief varieties and numerous subvarieties, about which considerable confusion still exists, especially when the attempt is made to classify them according to some rigid system. They are tumors in which connective tissue as well as epithelial elements are found side by side, both tissue-elements taking part in the new growth. Sometimes one and sometimes the other essential tissue type predominates. In those cases in which the connective tissue grows to predominate and the epithelium simply keeps pace to furnish the cover for the connective-tissue sprouts, it is evident that we are brought close on the border-line of such connective-tissue tumors as fibroma and myxoma, which grow from a mucous or cutaneous surface and obtain a covering of surface epithelium. Again, in those tumors in which the purely epithelial elements are largely in excess, the confines of certain kinds of malignant epithelial neoplasms (carcinomas) are reached. It should then be borne in mind that with the present class of tumors, as in many other varieties, absolutely specific differential characteristics cannot be set up. For this reason Ribbert's plan of describing under one common head the several varieties of this class of tumors has been adopted, since it does not commit itself to any particular scheme of classification.

The fibro-epithelial tumors, for convenience of description and for the purpose of utilizing the generally accepted terminology, may be divided into two principal varieties, based upon morphologic and histogenetic grounds. Those tumors in which *surface epithelium*, either cutaneous or mucous, participates, form one variety represented by the *papillomas*; while the neoplasms whose epithelium is derived from pre-existing glands or glandular remnants form the other main variety, the *adenomas*.

Papilloma.—For the most part the tumors belonging to this subdivision are, as the name indicates, "papillary" growths; that is, they tend to assume the form of a villous excrescence, projecting in the shape of a compound nodular mass above the surface from which they originate. In some of these tumors, especially those springing from the mucous surfaces, the growth is composed of a great number of delicate branching processes. The base of attachment of these masses is usually broad, though in some cases a very narrow pedicle serves to attach the tumor-mass to the surface from which it springs. Others of the papillomas are single protuberances, varying greatly in size. Again, there is a flat papilloma in which the tumor-mass is but little elevated above the surrounding surface.

Both hard and soft papillomas are found, those growing from cutaneous surfaces, like the common wart and the horny tumors, being generally more firm than those springing from mucous surfaces, although hard tumors are, for instance, found in the larynx.

As has been said, these tumors are usually situated on cutaneous and mucous surfaces, and are common in the skin at the orifices of the body, in the respiratory tract (especially the larynx and trachea), in the digestive tract, in the peritoneum, and in the genito-urinary tract. They are also found in the ducts of various glands. In the skin the ordinary examples

of the hard variety of tumors are the common wart, the dense cutaneous horns (*cornu cutaneum*), and the acuminate condylomas. Cauliflower-like growths seen in the urinary bladder and in the rectum are good examples of the soft papillomas; and the stomach and intestines are sometimes the seat of flat, papillomatous growths. Certain cysts, especially of the ovary, may become the seat of papillomatous growths in their interior.

The rate of growth in the harder tumors is generally slow, and they tend to remain at rest after attaining a certain size. Some of the soft, villous tumors grow rapidly, and become large enough to cause mechanic discomfort.

In structure these tumors consist of a vascular connective-tissue framework, upon which the epithelial elements are laid. The amount of this epithelial covering is subject to wide variation, and according to the locality from which the tumor springs we may find squamous or columnar epithelium covering the single or multiple connective-tissue sprouts. In the hard tumors of the skin the pavement epithelium is usually abundant, many-layered, and in various stages of horny transformation. In the soft, villous tumors the epithelial lining is thinner, sometimes being but a single layer of cells, and often these cells are but loosely attached to the supporting framework. This disproportionate relationship of the connective tissue and epithelium has given rise to the question whether the one or the other tissue forms the starting-point of the tumor.

That irritation, especially if long continued, is a potent factor in favoring the growth of certain of the papillomas is clearly proved. The condylomas or venereal warts appear especially about the penis, vulva, and vagina when these parts are the seat of an irritating venereal discharge or when some chronic inflammatory process is at work. It is highly probable that they owe their origin to some infectious agent, the nature of which is still obscure. Irritative factors can also be traced in some of the cutaneous warts and horns, and in certain cases a chronic inflammatory condition seems to underlie the development of papillomas in the larynx, the rectum, and the vagina. As congenital tumors the papillomas are rare; they have been found both in newborn and very young children, but an embryonic influence is hard to trace.

Adenoma.¹—In both macroscopic and microscopic morphology these tumors tend to reproduce the structure of glands or gland-like organs; that is to say, they are formations in which epithelium tends to arrange itself either in the form of tubules (*tubular adenoma*) or in acini (*acinous adenoma*), and in which the vascular connective tissue arranges itself to conform to the type of growth chosen by the epithelium.

Adenoma may grow in the substance of a glandular organ, and either take the type of the matrix or one foreign to it. It may also grow from free cutaneous or mucous surfaces. In the first instance it generally appears

¹ At first sight it seems easy to define as adenomas those tumors which tend to reproduce in their growth one or another of the types of glandular organs; but, as Lubarsch remarks, it is highly desirable, in accepting this definition, to be quite clear upon our definition of a "gland," and here an obstacle is encountered. Such secretory organs as the mammary, sweat-, and salivary glands, with the pancreas, liver, and glands of the digestive mucosa, are easily reconciled with our notions of what a gland really is; but in connection with the kidneys, adrenals, thyroid, hypophysis, the ovaries, testicles, and genital ducts, difficulties are met; in all these organs the characteristic elements may form tumors that are classed as adenomas. This shows how unsatisfactory the morphologic basis of definition and classification of tumors often proves.

as a more or less spheric mass, surrounded by a capsule. Upon free surfaces it tends to become compound, warty, or villous, resembling a papilloma, and usually styled papillomatous adenoma.

Depending upon the abundance and characteristics of the connective-tissue supporting substance there are both hard and soft adenomas; and in some examples spaces or cavities form, producing in advanced stages the large cysts of the subvariety designated as cystadenoma. The contents of such cavities and cysts vary considerably, being fluid, semifluid, or solid. There can be no doubt that some of these neoplasms produce the peculiar metabolic products of their glandular prototypes, although whether in the normal chemical and functional perfection is not yet known. For example, a fluid resembling bile is produced in hepatic adenomas, and colloid is formed in the alveoli of adenomas of the thyroid; and from clinical observations it

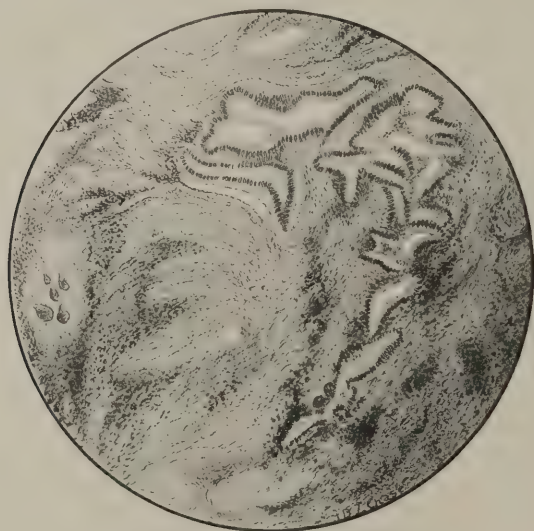


FIG. 59.—Tubular cystadenoma of the bile-ducts. $\times 35$.

seems that adenomas arising from adrenal rudiments give rise to the toxic products of the adrenal when it is functionally perverted.

Adenomas may arise in connection with any of the true glands or in the organs with a fibro-epithelial structure, and they appear not only in the substance of or in connection with pre-existing glandular organs, but often quite independently of them. Of the independent adenomas a great deal of interest is centered upon those which arise from secondary and displaced rudiments of the thyroid gland, and which reproduce quite typical thyroid structures in situations entirely outside of the normal location of the thyroid body; and in those cystic, solid, or papillomatous adenomas of the kidney or adjacent organs (the non-malignant hypernephromas) which have their origin in aberrant rudiments of the suprarenal gland.

The adenomas usually grow slowly, and rarely attain a great size. The tumors of the mucous surfaces and those in the liver, kidneys, testes, and

ovaries are often rapid in their growth, and may become quite massive. Cystic degeneration is not uncommon, especially in the new growths of the ovary, kidney, and testicle.

The encapsulated adenomas and the majority of those tumors appearing on free surfaces are of a benign nature. The papillomatous adenoma of the ovary or Fallopian tube may travel along adjacent peritoneal surfaces and produce disseminated growths. Other adenomas advance through lymph-spaces or tissue-spaces to considerable distances beyond the starting-point of the tumor. By breaking into blood-channels, adenomatous elements (for example, of thyroid adenoma) may be transported and reproduce their kind in distant localities, and this power of metastasis brings them closely in touch either with a variety of carcinoma (adenocarcinoma) or, in the case of hypernephromas, with sarcoma.

The development of adenomas from misplaced rudiments of the thyroid and adrenal glands furnishes one of the most convincing arguments for the embryonic theory of the origin of certain tumors, and no other explanation can be offered to account for such growths except that which ascribes them to proliferation of tissue-germs or rudiments of organs which have, in the course of development, been deposited out of their normal surroundings. Frequent demonstration of such aberrant organic rudiments of the thyroid gland and adrenal in adults, at the situations in which these tumors arise, makes this view reasonable. The adenomas are often also of congenital origin. In regard to adenomas in general, mechanic and irritative factors seem to play a predisposing role in some cases. A parasitic cause has also been suspected.

Cystomas.—We have already learned that a cystic metamorphosis, by which is meant the production of cavities, is an occurrence not uncommon in true tumors and in various degenerations. The adenomas are especially prone to this change, and that class of fibro-epithelial growths known as cystadenoma has many resemblances to the formations now to be discussed. Cystomas, cystic tumors, or cysts, as they are variously designated, may be defined as more or less spheric bodies, composed of a wall surrounding a cavity filled with fluid or semifluid contents. True cystoma is a new formation of cystic tissue (proliferation cysts). A large number of cystic new growths spring from misplaced embryonic rudiments, forming the cystic teratomas and dermoids.

The contents of the majority of true cystomas are fluid, resulting from the secretory activity of the lining cells or from transudation from blood and lymph-vessels. The fluid may take on a serous, mucoid, or colloid character; and cells in various kinds of retrograde change, like fatty and horny, may be present in the fluid. Further changes may take place in the cystic contents, resulting in the production of cholesterin, pigment, calcareous material, peculiar fatty products, and caseous material.

Closely related to retention cysts (page 117), though differing in origin, are the formations resulting from the persistence of fetal canals which normally become obliterated, and illustrated by cysts of the urachus, parovarium, spermatic cord, testicles (hydatids of Morgagni), and the suspensory ligament of the liver. Persistent or imperfectly closed fetal clefts may also give origin to cysts, as seen in the cystic hygromas of the neck in the former location of the branchial clefts.

As regards the proliferation cystomas, in some of them it becomes a difficult question to decide whether they should be regarded as cystomas in the

strict sense, or as fibro-epithelial tumors which have undergone cystic change. A common example of these cystomas is found in the ovaries, in which single, multiple, and compound (multilocular) cysts are found, often attaining large proportions. The ovarian cystomas are often complicated with papillomatous growths, generally projecting into the cavities, and are then called papillary ovarian cystomas. In a like manner the liver and kidneys may become the seat of single, multiple, and compound cysts, which sometimes attain a size sufficient to displace a part or the whole of the organ. The compound renal cystomas are generally of congenital origin, and aside from these the kidney may be occupied by single or multiple cysts, which recent studies indicate to have originated from misplaced remnants of the adrenals. Another organ in which cystomas are frequent is the mammary gland. Here, however, the new growth is often solid in parts which have an adenomatous structure, making a tumor which has been called adenocystoma; but single and compound cysts also appear here.

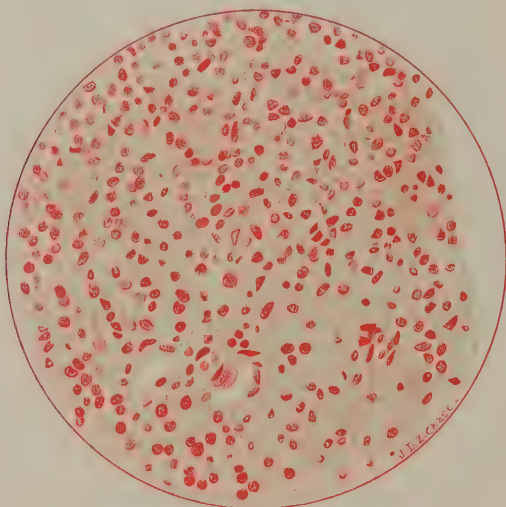


FIG. 60.—Glioma of the brain. $\times 335$.

Gliomas.—The central nervous system is the seat of a special kind of tumor—like itself, of ectodermic origin. These tumors are called gliomas, and have their beginning either in the elements composing the supporting tissue of the brain and spinal cord (the neuroglia) or from the cells lining their cavities (ependyma). In very rare instances real glioma may spring from the glia-layer of the retina. A great deal of confusion concerning the histogenesis of these tumors has been cleared up since the elaboration of specific stains for neuroglia (Weigert and Mallory) and for the nervous elements proper (Weigert, Pal, etc.).

The gliomas, while varying in size, rarely become massive; they may be single or multiple. Their color often resembles that of the surrounding nervous tissue, and their boundaries are rarely sharply defined, so that both a gross and a microscopic infiltration is found. Hard and soft varieties occur.

Microscopically either an extraordinary development of fibers with the special staining affinities of neuroglia, and few cells, or many cells and few fibers, are found. Incorporated in the substance of the tumor, in varying amounts, true nerve-tissue may be found, such as ganglion-cells and nerve-fibers. There is no positive evidence, however, that the nerve-cells and fibers proper proliferate in the tumor, so that such forms as "ganglionic neurogliomas" must at present be regarded as gliomas in which an unusual number of ganglion-cells and nerve-fibers have been included in the proliferating neuroglia, or as tumors in which ganglion-like cells without true nerve-branches are formed. Another point apparently settled by recent investigation is that in true gliomas mesodermic cell production does not predominate; hence the inaccuracy of such terms as "gliosarcoma." Furthermore, it now appears that most of the so-called gliomas originating in the retina, especially in young children, are in reality a form of round-cell sarcoma with pronounced metastatic tendencies, which glioma lacks.

While it has thus become possible to exclude certain neoplasms formerly classed with glioma, recent studies upon these tumors and upon neuroglia in general have given rise to other complications. The differentiation of true gliomatous tumors from other forms of pathologic neuroglial overgrowth, as seen in certain forms of sclerosis, of nodular gliosis, and of the central gliosis in syringomyelia, has become more difficult; indeed, it is not yet accomplished. The ependymal gliomas, the cellular elements of which have an epithelioid aspect similar to the normal cells lining the cavities of the central nervous system, in structure often simulate endotheliomas to a marked extent.

Upon a morphologic basis gliomas are classed into the richly cellular form (chiefly small, round glia-cells); the fibrillary form, with few cells and many well-developed neuroglia-fibers; the astrocytic or spider-celled; the spindle-celled; and the giant-celled varieties (Stroebe). The vascular supply of these growths is subject to wide variation. Some of the tumors are highly vascular, and it is not uncommon to find in them cavities of varying size filled with escaped blood, or cysts containing clear serous fluid from ancient hemorrhage. Such transformations as fatty and calcareous degeneration are sometimes seen, and an edematous and granular degeneration of the glia-cells also occurs.

We find both slowly and rapidly growing gliomas. They tend to infiltrate the substance of the brain and cord, but seem to respect such connective-tissue structures as the meningeal membranes, differing in this respect from sarcoma. They have no power of metastasis, unless we include with them the above-described doubtful tumors, retinal gliomas, which often give rise to secondary growths in such organs as the liver.

With the etiology of such pathologic affections of the brain and cord as disseminated sclerosis, nodular gliosis, and syringomyelia entirely obscure, and with our knowledge of normal neuroglia just in a phase of transformation, it is scarcely to be expected that much can be said upon the causation of glioma. An embryonic defect or aberration seems to be responsible for the origin of certain ependymal gliomas, especially the congenital ones. Traumatism is possibly a factor in some cases, and there is a growing suspicion that toxic or infectious agents will be found as essential causative influences, both in the various forms of gliosis and in the closely allied neoplasms, gliomas.

Neuroma.—This term has usually been applied loosely to all new growths containing nerve-cells or nerve-fibers in a fibromatous matrix, as, for example, amputation neuroma, multiple cutaneous and cirroid neuromas, which in a previous description we have properly looked upon only as fibromas of the peripheral nerves or of the ganglia, either of the cerebro-spinal or sympathetic system. Strictly speaking, a neuroma is a tumor composed of newly proliferated proper nerve-elements, either neurones or neuraxones, or both. It now appears that certain recently studied neoplasms can be included under this head.

Whether the so-called true neuromas of the spinal cord recently described (once in connection with syringomyelia, once in tabes, and again in an apparently normal cord, and in which there was an abundance of medullated fibers running promiscuously and having no apparent connection with the tracts of the cord) are real neoplasms or only artefacts, as Lubarsch suggests, is difficult to decide. But outside of the central nervous system some of the growths reported seem to fulfil all requirements, as, *e. g.*, the multiple dermal neuromas found by Knauss in young children. They contain both branching ganglion-cells resembling those of the sympathetic ganglia, and numerous medullated and nonmedullated fibers showing no anatomic connection with the nerves in the neighborhood, and apparently only to be explained on the basis of a proliferation of original nervous elements. Similarly the ganglionic neuromas show on careful histologic analysis with specific staining abundant ganglion-cells, apparently newly formed. These solitary ganglionic neuromas have been found in the thoracic, lumbar, hypogastric, and solar plexuses of the sympathetic, and also in the adrenal plexus.

THE SO-CALLED MALIGNANT TUMORS.

In the preceding discussion reference has several times been made to various properties of the so-called "malignant" tumors, and it now becomes our duty to study more in detail this very important class of neoplasms. They differ in their biologic activities, and especially in relation to their influences upon the host, from the so-called benign tumors. The term cancer is, in ordinary parlance, applied indiscriminately to all tumors which show the characteristics of malignancy; that is, to tumors the growth of which is unbounded and generally rapid, which tend to recur after operative removal, and which, above all, reproduce their kind in remote and often vital regions of the body, ultimately resulting in death of the patient. The malignant neoplasms are divided into two great groups, sarcoma and carcinoma, in each of which there are numerous varieties. We have already learned in the study of the preceding tumors that some of them may acquire certain of the properties of malignant tumors, like local recurrence, diffuse growth, and even the power of remote growth or metastasis, whereby they are brought closely in touch with the class of new growths now to be considered. In fact, the acquisition of one or more of the malignant characteristics in these otherwise benign tumor varieties is an occurrence which makes it very difficult to say just where the border-line is to be established between them and sarcoma and carcinoma.

It is generally customary to consider separately the two great varieties of malignant tumors, placing sarcoma at the end of the description of the connective-tissue varieties, and carcinoma after the fibro-epithelial tumors.

For the perfect types of sarcoma and carcinoma such a subdivision is quite appropriate, for no one would think of confusing a small round-celled sarcoma with a perfect adenocarcinoma. In the one case the mesodermic nature of the tumor-cells is plainly evident, and in the other the ectodermic or endodermic affinities of the proper tumor-cells are undoubted. In the intermediate subvarieties of sarcoma and carcinoma the difference is less striking, as seen in the case of the so-called alveolar sarcoma, or in the growths reproducing endothelial structures, or in those originating from the adrenals (malignant hypernephroma), in which the resemblance to certain forms of carcinoma is indeed striking, and in which it becomes exceedingly difficult to determine the histogenetic affinities. It is upon the morphologic basis solely that these two great varieties of malignant neoplasms have been differentiated, since in their life phenomena they have so much in common as to make a close distinction impossible.

That sarcoma and carcinoma do approach each other by easy gradients cannot be denied, and that there result a series of neoplasms, the place of which is upon the border-line between the two types, is also unquestionable. Perhaps it might be well to include them both under one head, as is done when the term "cancer" is used in its broad and popular sense. We must, however, look to the future to furnish us the only unassailable basis of classification for these as for all other true tumor varieties, viz., the etiologic one.

It is quite possible that we shall then find all the malignant neoplasms to possess a specific characteristic; but as our knowledge now stands, and for convenience of description, we must endeavor to recognize the morphologic distinctions of the perfect types of the two varieties, and consider them accordingly.

SARCOMA.

General Considerations.—Sarcoma is a malignant tumor of the connective-tissue type, the elements of which do not reach the morphologic perfection of mature and normal structures. The unfinished or embryonic condition of the tumor-elements, like that seen in developing mesodermic tissue or in granulation-tissue, has been looked upon as a peculiar feature of sarcoma. This definition is not sufficiently elastic, for there are subvarieties of sarcoma the elements of which do reach a high degree of morphologic perfection, and there are those in which the structure recalls more vividly epithelial than connective-tissue features.

Another differential point for separating sarcoma from carcinoma, upon which much stress has been laid, is the preponderance of the cellular elements over the intercellular substance in sarcoma, as compared with the relatively greater development of the framework or *stroma*, as it is called, in carcinoma. Here again careful study fails to emphasize this peculiarity, for many forms of sarcoma show a well-developed stroma in which a proper sarcoma body or "parenchyma" can be easily distinguished from the supporting framework or stroma.

Anatomic Features.—The gross anatomic features of sarcoma are by no means uniform. The size of the tumors differs according to the locality in which they appear and according to their peculiar structure. In the case of sarcomatous growths arising in connection with bone, it is not uncommon to find them attaining large size; while, on the other hand, the secondary foci of some varieties, especially pigmented or melanotic sarcoma, may be

so small as to appear dust-like, and may be diffused throughout an entire organ, or over a large area of free surface like the peritoneum. The original or primary growth is usually a single one, and the tendency is to assume a spheric shape; some, as chloroma and certain endotheliomas, grow as flat or plate-like masses. In the unpigmented forms the growth is either colorless or of a faint pinkish or grayish hue; but the highly vascular varieties are blood-tinged, while the pigmented forms may appear black, brown, bluish, green, or slate-colored. As compared with the average benign tumor, the consistency of sarcoma is soft, although examples are found with varying grades of hardness, culminating in growths with the consistency and nature of bone. The color and consistency of sarcomas may lack uniformity even in a single example, due to such factors as localized increase of blood-vessels, and hemorrhagic, fatty, mucoid, or other form of degeneration, sometimes even leading to the formation of cysts.

Histology and Histogenesis.—The data furnished by the histologic examination of sarcoma enable us to subdivide them according to the morphology of the tumor-cells. One large group has cells which uniformly tend to assume a spheric shape, giving the subvariety round-celled sarcoma; on the same basis the spindle-celled and the giant-celled forms may be differentiated; endothelioma and melanoma may be defined as distinct sub-varieties. The special morphology of these subvarieties will be separately discussed, but it is desirable to consider here some of the general histologic features of the sarcoma-cell.

In the attempt to demonstrate the specific nature of the sarcoma-cell, its various structural features have been successively reviewed, and some valuable acquisitions have been made to our knowledge of the cytology of tumors. In regard to the cytoplasm, it has been shown that the cytoplasmic constituents are subject to deviation in different varieties. In the spindle-celled, compact tumors the cytoplasm presents a distinct series of intracellular fibrils arranged to correspond with the long axis of the cell, with comparatively few and very small cell-granules. In richly cellular softer spindle-celled forms the fibrils are less pronounced and the granules better developed; while in giant-celled sarcoma and in many other well-developed forms scarcely a trace of fibrillary structure remains in the granular protoplasm. It would seem that the cells of the firmer and usually least malignant types attain nearest to the morphologic perfection of mature connective-tissue cells, while the more decidedly sarcomatous types fail to reach this stage.

It has been thought by some authorities that the poverty of nuclear chromatin was a specific characteristic of the sarcoma-cell, showing its reversion to the embryonic type; but more extended study fails to confirm this view, since all grades of chromatin production can be found in the nuclei of various sarcomas. The same consideration holds true for the nucleoli, of which there may be one or several. It is not uncommon to find massive sarcoma-cells with richly developed chromatin (hyperchromatosis), but even these have been found in other tumors and pathologic formations, and they appear to indicate stagnation or degeneration of the cell and nucleus. Some of the most marked examples of chromatolysis, or dispersion and solution of nuclear chromatin, are to be seen in certain richly cellular sarcomas, from the aggregation of the nuclear material into irregular masses to its breaking-up into dust-like particles and final disappearance. The dichromophilism of

the nucleolus and chromatin, by which is meant the different selective staining of these two structures in a mixture of anilin dyes (red and blue, for instance), while beautifully brought out in sarcoma-cells by the use of certain staining combinations, is not a distinctive attribute, being also observed in other cells.

The process of nuclear and cellular division in the sarcoma-cells proceeds both by regular and irregular methods. Karyokinesis or indirect segmentation is the rule, although it may deviate from the normal in various ways, and sarcoma-cells with asymmetric and pluripolar mitoses are frequently seen; although here again there is nothing that can be said to be peculiar to this variety of cell. Direct segmentation (amitosis) is a relatively frequent method of nuclear division.

Leukocytes, both of the polymorphonuclear and mononuclear forms, are present in varying amounts in sarcoma. Plasma-cells are frequently found at the border of the growing tumor, and mast-cells may also be seen. The function of the leukocytes is not entirely clear, though they are known to gather not only in the tissue-spaces and blood-vessels of the intercellular tissue, but also to invade the proper tumor-cells. They are especially abundant about necrotic foci, and the most reasonable interpretation of their presence is to ascribe to them the role of phagocytes, engaged in disposing of the degenerated products resulting from the breaking-up of the nuclear chromatin and the death of the cell. Distinct purulent foci are occasionally found, and are probably the result of a bacterial infection of the sarcomatous tissue.

The disposition of the denser spindle-celled subvarieties of sarcoma is to grow slowly, and often to produce a rough capsule by which they are separated from the mother-tissue. Such tumors may grow for months and years with little evidence of malignancy, but their true nature is often shown when, after some traumatism or other irritating influence, they suddenly grow rapidly, and sometimes give rise to an extensive crop of secondary deposits. Even the more rapidly growing and destructive types may become arrested and remain latent for a varying period, when they unexpectedly assume malignant properties. For the most part, the richly cellular forms grow with great rapidity.

Metastasis.—The sarcomas possess the capacity of metastasis. This function is not a universal one in them, however, for some varieties never reproduce new growths outside of their primary abode—in this respect differing from carcinoma, which more uniformly tends to metastatic reproduction. Still, this occurrence is often seen in sarcoma, especially in the richly cellular and rapidly growing varieties, and at times the vast number of secondary growths which originate from a primary focus is almost beyond belief. The secondary deposits may appear in such mesodermic structures as the subcutaneous tissue, fascia, bones, and muscles; or in the viscera, like the liver and lungs. In general, the secondary tumors reproduce the typical structures of the primary growth. Dissemination of the elements giving rise to metastases, while more often taking place by the blood-vascular system, is not limited to it, for the lymph-channels may also serve as the pathway of transportation.

Blood-vessels.—While an abundant development of blood-vessels is a common occurrence in sarcoma, this feature is liable to considerable variation. The blood-vessels in the stroma may be histologically perfect, they may be simply distended tubes bounded by a single layer of endothelial

cells, and in some instances even this endothelial layer seems to be absent, and the blood coursing through channels bounded solely by the tumor-cells. In the highly vascular forms, free hemorrhage into the tumor-substance is often seen. Other forms of degeneration, like fatty, mucoid, hyaline, and cheesy, are not uncommon; and certain substances giving the microchemic reactions of amyloid or glycogen are at times present.

Age.—Sarcoma is especially the malignant tumor of childhood and young adult life, differing in this respect from carcinoma, which commonly appears after the fortieth year. It may, however, occur at any age.

Sites.—The usual sites are the fascia, subcutaneous tissue, muscles, bones, articular cartilage, meningeal membranes, and more rarely the viscera, like the kidneys, liver, and lungs. The tumor may also grow in pigmented and unpigmented birthmarks or nevi, either of a blood-vascular or lymph-vascular structure. It is as though these transformed foci, already on the way toward mesodermic tumor-growth, furnished an especially favorable soil for a sarcomatous proliferation. Sarcomas often occur in places exposed to traumatism, at the seats of scars or of irritation from pressure and inflammation. But in addition to the nevi, the scars, and the areas of traumatism, there must be something more to result in the production of a sarcoma, for only a few of these defective localities become the seats of such tumors; and besides this, it must be remembered that sarcoma more often appears in situations in which no such previous changes have occurred. The underlying factor is apparently as far from being definitely answered in the case of sarcoma as with tumors in general.

Etiology.—Of all the theories advanced in the study of this problem, however, the one which ascribes to a parasitic influence the exciting agency in sarcoma seems best to meet the conditions of our present knowledge. There is so much in common between sarcoma and certain lesions resulting from known infectious agents, the infective granulomas, that we are justified in the hope of ultimately finding parasitic agents here as well. Of the investigations, that centered upon the blastomycetic fungi seems now to be most promising, since the presence of particular yeast species has been demonstrated in sarcomatous tumors, and by cultural methods these organisms have been isolated in purity, and by comparative inoculation experiments they have been found to produce new growths. None of them, however, could on rigid histologic analysis be pronounced sarcoma.

The Varieties of Sarcoma.—**Spindle-celled Sarcoma.**—One of the most common sarcomas is that made up of more or less elongated or spindle-shaped cells—the so-called spindle-cell sarcoma.

The tumors vary in size and tend to assume a globular shape, especially when their growth is unconfined. The new growth is generally white or only slightly tinged with color. Both hard and soft kinds are found. Their growth is usually slow in the case of the denser masses, and more rapid in that of the soft ones. Often an imperfect outer fibrous layer separates the tumor from the structures bounding it; this is particularly the case in the hard tumors. On macroscopic sections the surface may be uniform, or it may be broken by islands of an osseous nature, by spicules of bone, or by masses of calcareous substance. Foci of softening or of degeneration are not uncommon. The primary growth is usually found in the localities in which spindle-celled connective tissue pre-exists.

There is no rule about the metastasis of this variety, for some of the

that give rise to the confusion concerning the sharp demarcation of sarcoma and carcinoma. These alveolar sarcomas may be of endothelial origin, belonging to the endotheliomas.

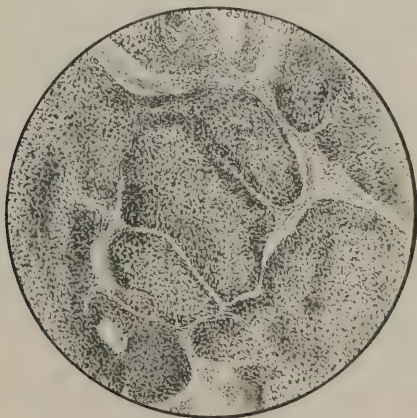


FIG. 65.—Alveolar sarcoma. $\times 55$.

In some of the round-celled sarcomas there is a distinct reticulum resembling that of lymphadenoid tissue; such tumors are called lymphosarcomas.

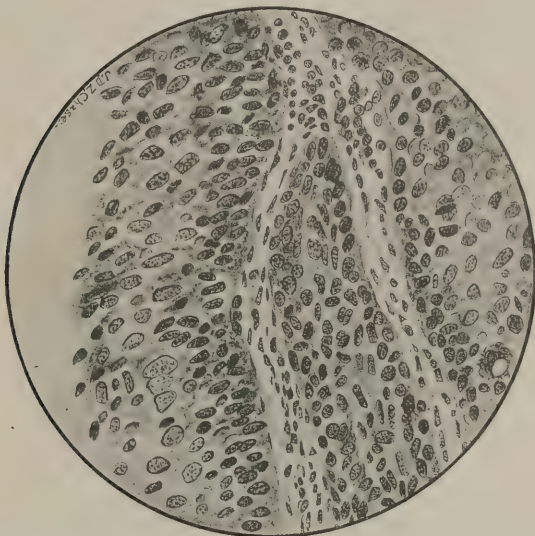


FIG. 66.—Alveolar sarcoma. $\times 335$.

They occur most frequently in lymph-glands and the spleen, also in the pituitary body.

Giant-celled Sarcoma.—While multinuclear cells are not uncommon in

neoplasms never to reach the advanced stage found in the harder example of spindle-celled sarcoma (fibrosarcoma). In one form of large round-

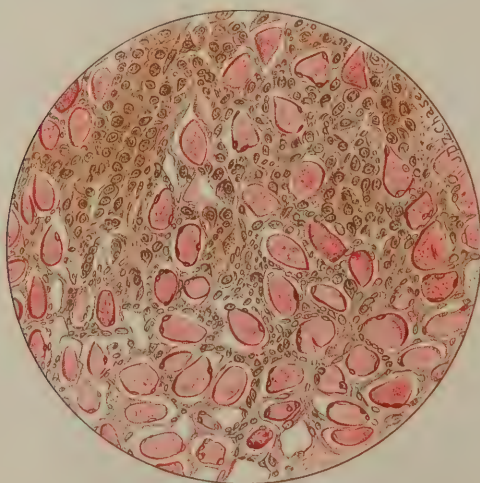


FIG. 63.—Round-celled sarcoma invading muscular tissue. $\times 300$.

celled sarcoma the tumor-elements take on the aspect of epithelial cells (epithelioid or endothelioid), and these cells arrange themselves in well-

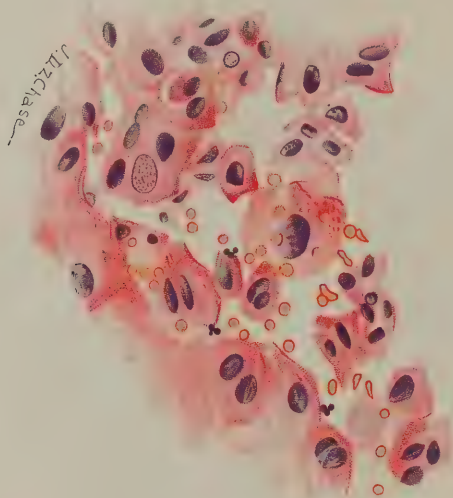


FIG. 64.—Large round-celled sarcoma. $\times 500$.

localized groups, separated from each other by a distinct stroma. These are the *alveolar sarcomas* described long ago by Billroth, and it is such forms

giant cell. Both normal and abnormal segmentation and fragmentation of the nucleus are seen.

The newly formed blood-vessels of the tumor proper generally develop poorly, and scarcely reach a more mature stage than that seen in young granulation-tissue; *i. e.*, an endothelial tube surrounded by the tumor-cells. When well-formed arteries and veins are found, they can, for the most part, be regarded as pre-existent vessels of the matrix.

Spindle-celled sarcomas of perivascular origin often reproduce an imperfect kind of bone, in which the tumor-cells are found lying in anastomosing spaces where bone-corpuscles normally exist, and in which the ground-substance is more or less homogeneous and the seat of calcareous deposit. Those spindle-celled tumors in which calcification occurs in the ground-substance are called osteosarcomas; those in which the ground-substance

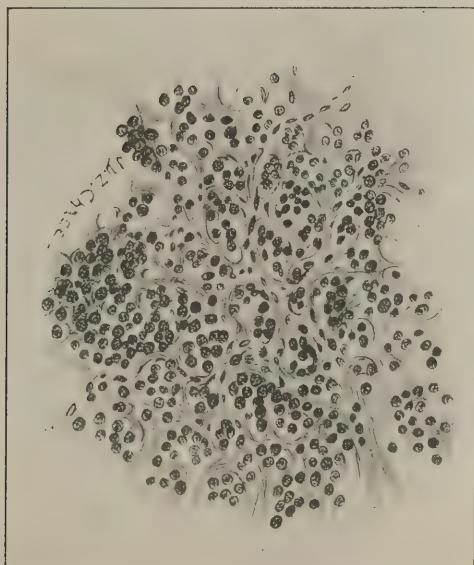


FIG. 62.—Round-celled sarcoma. $\times 200$.

takes the aspect of bone, but in which calcification fails, are distinguished as osteoid sarcomas.

Round-celled Sarcoma.—This is a sarcoma composed of small round cells. It grows more rapidly, and is generally softer and more malignant than the spindle-cell sarcoma. It is found in the same localities, and also occurs in the testicle and kidney.

There is a large-celled and a small-celled form of round-celled sarcoma; in the large-celled examples, polymorphous elements with oval, spindle-shaped, and irregular forms are not uncommon. Considerable difference in the amount of intercellular substance is found, some small-celled tumors being composed almost wholly of closely packed cells, with but a trace of intermediate supporting substance, while in others a distinct stroma can be made out. The rule is, however, for the intercellular substance in these

growths pursue an essentially benign course, while others have all the attributes of malignancy.

Microscopically it is possible to distinguish differences in the size of the tumor-cells, enabling us to differentiate large and small spindle-celled sarcoma; in the amount of intercellular substance, which, when abundant and distinctly fibrillary, gives the so-called fibrosarcoma, or, when the seat of mucoid metamorphosis, the myxosarcoma; and in the abundance of blood-vessels. Ossous or osteoid tissue is occasionally present, giving rise to the osteosarcoma or osteoid sarcoma.

A very ready method of studying these tumors is in fresh-teased preparations, in which the individual cells can be observed. It will be found that in the soft and richly cellular forms the cells are usually much elongated, and taper to delicate end-processes, and that the proper tumor-substance is made

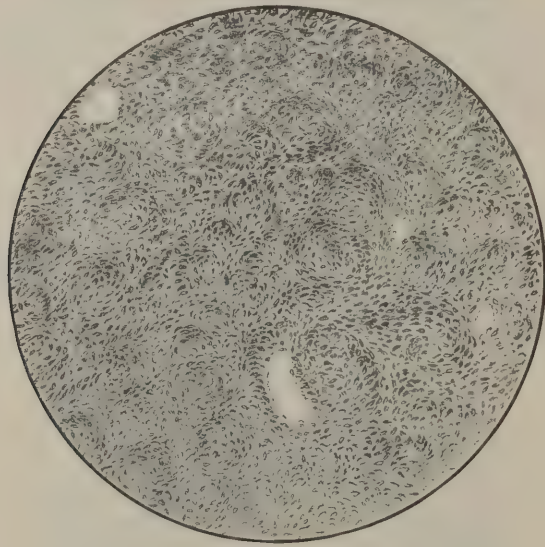


FIG. 61.—Spindle-celled sarcoma of the choroid. $\times 153$.

up of these elements closely set, and with very little, if any, supporting substance between. Very frequently these cells dispose themselves parallel to the blood-vessels, as though choosing their walls as a support; but at other times the cells may arrange themselves in lines of growth that show no evident preference for the direction of the blood-channels. In the small-celled tumors, the elements are quite uniform in size and appearance; while in those with large cells, variability in shape—polymorphism—is more marked, and it is not uncommon to find a mixture of spindle-shaped, oval, and round cells of varying size. The nuclei are ovoid in the small-celled forms, and provided either with a small amount of chromatin, making a poorly defined network, or with a compact mass filling the nucleus; but in the large cells the nucleus may exhibit a well-formed and abundant chromatin framework with one or more nucleoli. The nucleus may be irregular in outline, and even subdivided into numerous accessory nuclei, producing a multinuclear or

the large-celled examples of both spindle-celled and round-celled sarcoma, there is a class of sarcomatous growths in which giant cells are uniformly found in such numbers as to give a characteristic stamp to the tumors. This is not to say that the multinuclear cells are the sole tumor-elements, for besides them we find both spindle-shaped and round cells; the giant cells are simply uniform morphologic features of the new growth, and are present in considerable numbers. Giant-celled sarcoma is also called myeloid sarcoma or myeloma.

The typical neoplasm of this variety is the growth arising in connection with the inferior maxillary bone, especially of children, making one of the forms of epulis, malignant epulis. It is not apt to give to metastasis, while other giant-celled sarcomas not rarely do so.

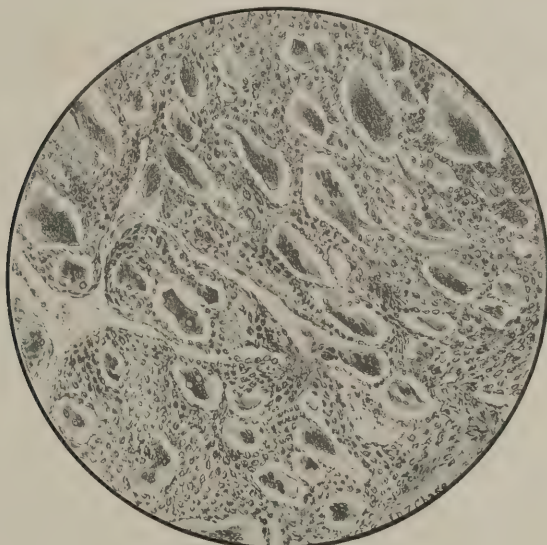


FIG. 67.—Giant-celled sarcoma. $\times 135$.

Most of the giant-celled sarcomas arise in connection with the osseous system, either from the periosteum or from the bone-marrow, but they have been found in the mammary and thyroid glands.

The tumor is composed of round or spindle-shaped cells of varying size arranged about the giant cells, which are large protoplasmic bodies containing many nuclei, not rarely one or more clear vacuoles. There is, as a rule, very little stroma in these growths. The giant cells vary in shape, sometimes having an unbroken circular or oval outline in section, again being decidedly irregular, with the outline broken by offshoots or protoplasmic processes extending in various directions. Their nuclei are sometimes small and extraordinarily numerous, even reaching hundreds in a single cell; other times they are larger, more liberally supplied with chromatin, and not so numerous; while in still other examples a massive nucleus with little evidence of subdivision is seen. Often the nuclei are gathered at one pole of the cell, leaving a clear protoplasmic field at the opposite side,

just as is seen in the giant cell of tubercle. Various inclusions may be found in the substance of the giant cells. The giant cells are usually surrounded by a clear space of varying width, probably as the result of shrinking in the process of hardening the tissue.

The methods by which this remarkable subdivision of the nucleus is brought about are, for the most part, direct segmentation and fragmentation, although some cells show the nuclear figures of karyokinesis, usually in the stages of pluripolar or asymmetric division.

The origin of these peculiar multinuclear cells is an interesting problem. There can be little doubt from recent studies that some of them are to be regarded as phagocytes, the function of which is to remove various foreign substances, an assumption which is strengthened by finding masses of blood-pigment, of hyaline, amyloid, or glycogenic material in their interior. Perhaps some of the cells arise by confluence of smaller ameboid endothelial cells, as has been suggested in explanation of the origin of other giant cells, and as would appear possible from the peculiar protoplasmic offshoots sometimes seen in these giant cells.

Melanotic Sarcoma ; Melanosarcoma ; Melanoma.—This is a pigmented sarcoma, the pigment being melanin.

The naked-eye appearances are usually most striking. The tumor varies in size and shape and is generally soft and friable, but can be distinguished readily by its pronounced color, which in the ordinary example varies from a dead black to a grayish hue. The shade of color varies not only in different tumors, but often in different parts of the same tumor, for portions quite colorless may lie close beside those which are as black as coal. The vascular supply of the tumor is sometimes very rich, and areas of hemorrhage are at times found. In some of the secondary melanomas, particularly those encountered in the liver, a peculiar liquefaction of some of the tumor-masses may take place, probably the result of a diffuse necrosis.

The primary seats of the melanotic sarcoma are especially such regions as normally contain pigment, like the skin and the choroidal layer of the eye. The tumors have a marked tendency to grow in areas of the skin the seat of birthmarks, the pigmented nevi or moles. Melanomas are also found in viscera and in connection with bones, and are either periosteal or medullary in origin ; but it is quite doubtful if, in these instances, the primary tumor (perhaps exceedingly small) growing from a pigmented region has not been overlooked, so that these osseous and visceral tumors are really metastases.

From the histologic standpoint it is possible to distinguish two kinds of melanotic sarcomas : those with spindle-cells and those in which the cells are epithelioid in morphology and in which a stroma separates them into groups or alveoli, like alveolar sarcoma. The spindle-celled tumors originate especially in the choroid of the eye, and reproduce these elements in their secondary growths, which attack the liver by preference. The skin is usually the seat of the alveolar melanotic sarcomas, and the tumors growing from nevi are apt to follow this type. Unna makes a strong argument for the epidermic origin of cutaneous melanomas springing from pigmented nevi ; while Ribbert regards them as arising from mesodermic pigmented cells (chromatophores). Recent investigations seem to corroborate the view of Unna. Round cells and giant cells may be found in the melanotic tumors of bone.

The pigment appears in dust-like particles, in larger granules, and some-

times in good-sized masses. The individual granules are highly refractive and of a yellowish tinge, so that they are readily seen either in fresh preparations or in stained sections. The deposit of pigment shows microscopic as well as macroscopic variations. In the alveolar growths the tendency for the granules is to collect in certain cells at the periphery of the cell-groups, near the stroma in which the blood-vessels lie, or even in clusters about the blood-vessels, due probably to the ameboid movement of the chromatophores or pigment-cells. In the choroidal tumors the pigment is more uniformly deposited in all the cells. In some secondary growths, more especially those in the liver from the choroid, the pigmentation may be so intense as to cover the cells and make it almost impossible to recognize them in microscopic sections; here also a further step leading to the liquefaction above noted is taken, when the cells die and leave only a granular protoplasmic detritus mixed with an abundance of pigment-granules. The pigment is often carried away from the tumor. Some of the cells in both cutaneous and choroidal melanoma possess several processes, one or more of which extend to a considerable distance as a tube-like prolongation containing pigment-granules and strongly resembling chromatophores (Depuè).

As regards the nature and source of the pigment in these tumors, much doubt still exists. It was at one time supposed that it was derived from the blood-coloring matter, but this is very questionable, especially as it is rare to find this substance giving the usual iron reaction of blood-pigment. Careful chemical analyses have been made of it, and while observers are not agreed upon certain fundamental points, especially as to the presence of iron, it seems to be established that the pigment contains a considerable proportion of sulphur. It is probable that the chemical nature of the substance differs in tumors originating from different localities, and that it is a product of the chemical activities of the tumor-cells themselves.

Chloroma.—Another pigmented tumor with some resemblance to the small-celled sarcoma usually known as lymphosarcoma is the quite rare and very remarkable chloroma. This, which is characterized by a peculiar greenish color, originates for the most part in connection with the bones (skull, vertebra, and humerus), generally in intimate relationship with the periosteum. The tumors have been found in lymphatic glands, in the liver, kidneys, and in the marrow of the bones, as metastatic growths. In connection with the bones they usually form flat, plate-like masses, often extending over large areas. The color is light green, dark green, grayish, or even yellowish, being most intense when the tumor is first removed from the body, and fading on exposure to the air or in various preservative solutions.

Histologically chloroma is composed of round cells resembling the small or large lymphocytes, with a delicate reticulum, strongly resembling the appearance of lymphoma. The pigment is not pronounced in sections of hardened tissue, but can be made out best in sections of the fresh tumor or in freshly teased preparations, when it appears in the form of highly refractive granules within the tumor-elements. The chemical nature of this coloring matter is still obscure, though there is reason for believing that it is in some way combined with fat, of which the cytoplasmic granules seem to be composed. The tumors are well supplied with blood-vessels.

The weight of opinion at present concerning the nature of chloroma is to regard it as a disease of the lymphadenoid system, showing certain affinities with leukemia and pseudoleukemia. The clinical course, while closely resem-

bling that of malignant lymphoma or lymphosarcoma, is in some respects different. These neoplasms belong to the class of sarcomatous new growths, for which a parasitic cause will perhaps ultimately be discovered.

Endothelioma.—This subvariety of sarcomatous tumors has gradually become defined, although many points relating to it are still in dispute. The present tendency is to include among the endotheliomas many of such anomalous forms of sarcoma as angiosarcoma (Fig. 69), psammoma, myxosarcoma, perithelioma, and cylindroma.

The endotheliomas are separated from other sarcomas on histogenetic and morphologic grounds. They include all those tumors arising from endothelial cells, no matter how they may subsequently be transformed. Thus it is evident that the endothelium of the blood-vessels and of the perivascular lymph-spaces, of the lymph-vessels, and of the great serous cavities (peri-

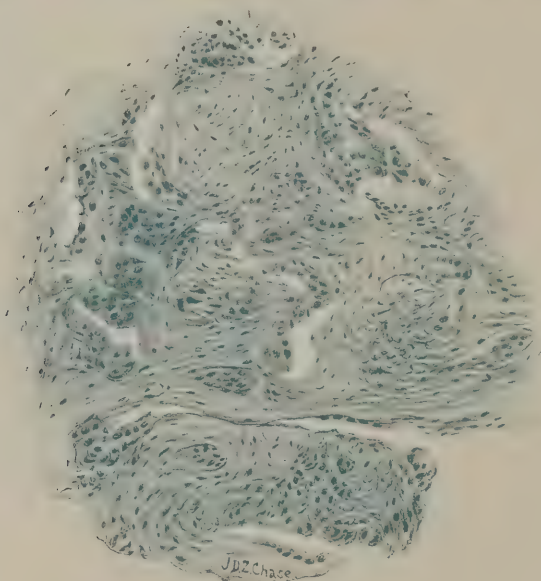


FIG. 68.—Endothelioma of the pleura. $\times 145$.

toneum, pleura, meninges) may furnish the elements of these neoplasms. When the close morphologic resemblance between endothelial and epithelial elements is recalled, it can be readily understood why endothelioma and carcinoma are often confused; and there is the additional fact that, even in such matters as the amount and disposition of the stroma, no essential histologic difference can be shown between some of the examples of these two tumor varieties.

The essential tumor-element is the round, flat, or cubic endothelial cell, often called, from its resemblance to epithelium, "epithelioid." Depending on the particular structure from which the first proliferation takes place, the tumor-elements arrange themselves in various ways. In those of blood-vascular (endovascular) origin the cords of tumor-cells often proceed in lines

strongly recalling the original vascular network, and in some of the recent stages it is possible to describe the thickened endothelium, the remains of the proper vessel-wall, and even to find blood-elements in the lumen of the proliferating endothelium, this lumen remaining more or less evident in the mass of endothelial cells or becoming obliterated. In endotheliomas of lympho-vascular origin, essentially the same appearance is found. When the growth departs from the endothelium of the lymph-spaces of the tissues, a more pronounced alveolar structure is produced, with anastomosing cords and nests of epithelioid cells surrounded by a well-defined connective-tissue stroma, with more irregular lines of growth than are seen in the other types. Depending upon the nature and amount of this stroma, the alveolar endothelioma presents examples with but little ground-substance of a finely fibrillar character, intermediate types with well-defined stroma, and others

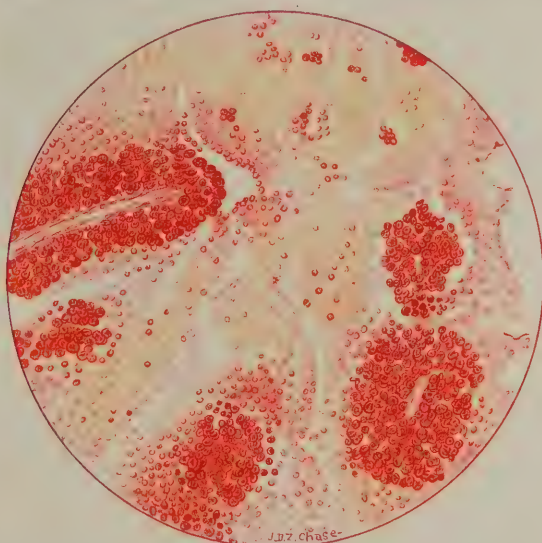


FIG. 69.—Plexiform angiosarcoma of the eye. Extensive areas of degeneration infiltrated with blood are seen between the sarcoma-cylinders. $\times 135$.

with abundant coarse, fibrous supporting tissue crowding the endothelial cells into narrow communicating clefts or causing them to disappear.

The stroma of some endotheliomas is subject to metamorphoses of various kinds. A myxomatous alteration produces the kind of tumor often called a *myrosarcoma*. In another variety, usually originating from the blood-vascular endothelium, a hyaline transformation of the vessel-walls and of the stroma produces the peculiar growths called sarcomatous *cylindromas*.

The dense endotheliomas of the dura represent endothelial new growths in which the stroma has become densely fibrous, and in these tumors spheric calcareous concretions of a laminated structure are often found, apparently identical with the so-called "brain-sand" normally present in the meninges and pineal gland; hence they are called *psammomas* or "brain-sand" tumors. In older tumors of this character the dense stroma has often so overgrown the endothelial elements as to make their recognition difficult; but in

newly developed psammomas a distinct endotheliomatous structure can be made out.

Certain members of this variety of sarcomatous tumors grow very slowly, show little or no tendency to invade surrounding structures, and rarely if ever produce secondary growths; this benign form of endothelioma is exemplified in the dural psammoma. On the other hand, there are endotheliomas which grow very rapidly, forming large primary tumors which encroach upon

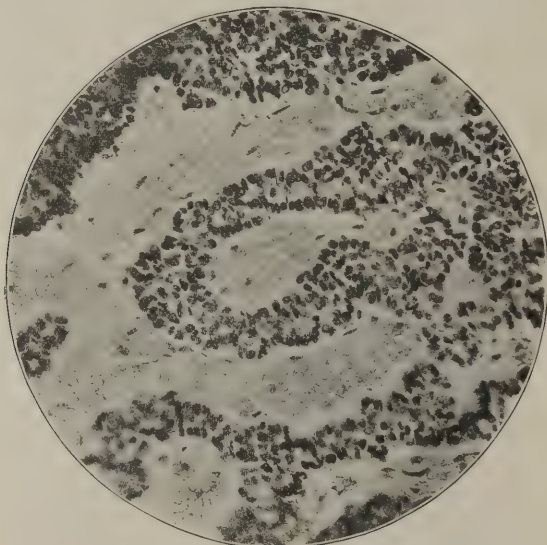


FIG. 70.—Endothelioma of the dura mater. $\times 200$ (Karg and Schmorl).

the surrounding tissues, and which reproduce their kind in metastatic growths in various regions of the body.

Occasionally a pronounced phagocytosis is observed in some of the sarcomas, the process being carried on by the tumor-cells themselves or by large macrophages.

CARCINOMA.

General Considerations.—We are now confronted with a large and important group of new growths springing, for the most part, from elements of ectodermic or endodermic origin; although it is generally accepted that tumors of this variety may arise from the cells of such organs as the kidneys and the sexual glands, organs which are of purely mesodermic origin. The parenchymatous elements of these tumors are of epithelial derivation, springing from the pavement-cells lining the cutaneous and mucous surfaces, from the cylindric cells covering large areas of mucosa, or from the cells making the acini of glandular organs and lining their ducts. It has already been stated that the fibro-epithelial neoplasms may approach the confines of carcinoma. In a way, a carcinoma can be regarded as a papilloma or an adenoma which has “gone bad”; that is, has acquired properties which impel it to break through its surroundings and to grow in a way that

departs from the tendency shown by the benign fibro-epithelial tumors. For example, an adenoma of the breast reproduces with some morphologic fidelity the normal glandular acini; a carcinoma of this same region fails to produce so perfect a structure. Hence it is that the carcinomas have often been designated as "atypical" fibro-epithelial neoplasms. Here, as elsewhere in the domain of biology, it is not an abrupt step which leads from the one to the other species—there is always an intermediate ground on which the widely divergent types are brought together; and thus it happens that there are papillomas and adenomas which assume more and more of an atypical growth until they must be regarded as carcinomas, and there are carcinomas the structure of which is so orderly as to resemble that of an innocent fibro-epithelial growth. We are still ignorant of the influence of such factors as heredity, environment, the mechanics of cell growth and proliferation, and the exciting causes which must play the same parts in relation to the pathologic formations known as tumors that they do elsewhere in biology; and, with no well-established laws to guide us, we grope in the dark when attempting to account for the variations, just as the zoologists once did with respect to animal species.

Manner of Growth.—The carcinomas which grow from free surfaces generally tend to take on a papillomatous or villous aspect, producing the so-called "cauliflower growths." Sometimes the surface growths are roughly nodular, again they are more thickenings of a flat surface. In the substance of organs, a more pronounced tendency to nodular growth is shown. The beginning of a carcinoma—in such a locality as the lip, for instance—is usually indicated only by an ill-defined thickening and hardening, and even in the advanced tumor this failure to be sharply demarked from the bounding tissues is usually shown. The same infiltrating tendency characterizes most of the growths of visceral origin, so that it is often impossible for the eye to separate the normal from the abnormal tissue, and even the microscope shows islands of tumor-cells far beyond the apparent boundaries of the growth. It is as though the tumor-elements were poured into the tissues in a molten state, and, by virtue of their fluid condition, permeated in all directions the spaces and clefts existing naturally in the tissues. The direction of growth or infiltration is modified by the character of the tissues bounding the carcinoma. In such structures as are soft and loose-meshed the outlying boundaries are more extensive than is the case when dense membranes or osseous or cartilaginous structures are encountered by the growing tumor. A very curious spectacle is often presented in the attempt of these growths to overcome cartilaginous or bony obstacles, in that they grow against them and produce a pressure necrosis, instead of invading them directly, while at the same time availing themselves of every possible channel presented by softer portions to advance by infiltration. In this way extensive and irregular tumor-masses are produced, and in advanced growths it is not uncommon to see all the structures in a given region of the body, as the neck, for instance, bound into one great diseased mass, the cement being composed of carcinomatous tissue growing in every direction. Petersen has recently studied the growth of carcinoma by the method of plastic reconstruction, and finds two types of growth: one in which the tumor grows from a single center, sending out processes in various directions, and one in which the growth springs from multiple centers.

Another phenomenon especially characterizing these neoplasms when

growing from free surfaces is necrosis of their superficial portions, resulting in ulceration or erosion. After the main tumor-mass dies and liquefies, it leaves a ragged and dirty ulcer, at the edges of which is a thickened ring. The necrotic processes are attended with the formation of pus, of false membrane, and of various kinds of fluid or solid detritus, and the development of putrefaction, often with most repulsive odors.

General Characteristics.—There is nothing about the color of carcinomatous neoplasms that serves to distinguish them from other tumors. That same whitish, grayish, or pinkish hue noted in so many other tumors is observed in them. There are certain cancers¹ that exhibit pigmentary deposits. When growing into fatty tissue, the islands of cancerous new growth can sometimes be easily detected with ordinary vision on account of a peculiar pearly luster which contrasts sharply with the yellow fat.

While there is really no limit to the size attained by the tumors of this variety, they do not, as a rule, become very large—principally, no doubt, because from their baneful influences the patient fails to live the necessary time. But good-sized masses are often found; and in other cases, especially when metastases are formed, the tumors may be extraordinarily numerous, causing an enormous enlargement of the affected organ.

Both soft and hard carcinomas are found, the difference depending for the most part upon the proportion of parenchyma and stroma. The very soft, richly cellular examples of glandular origin have often been called “medullary” or “encephaloid” cancers from their brain-like consistency, while the harder variety with well-developed fibrous ground-substance is called “scirrhus” cancer or scirrhus. The consistency of individual tumors is also influenced by various degenerations and metamorphoses to which carcinoma is subject.

The vascular supply which finds its way to the tumor by the stroma varies in amount; some are highly vascular tumors, and some have comparatively few blood-vessels and lymph-channels. The soft tumors may be so well supplied with blood and lymph that they yield a fluid on slight pressure or upon scraping the cut surface; and this fluid, or “cancer-juice,” as it is styled, is composed of tumor-elements mixed with blood-cells and lymphatic corpuscles. The lymph-trunks leading from a rapidly growing cancer may become enormously dilated, and on incision yield a cancer-juice.

Sites.—Primary tumors have the following habitats, given in their order of frequency (Birch-Hirschfeld): The uterus (especially the vaginal portion); the external skin (lower lip, more seldom the lobe of the ear, eyelids, cheek, and extremities); the female mammæ (much more rarely the male breast); the stomach (pyloric region, more rarely the cardiac end, and most rarely the fundus); the rectum; the esophagus; the ovaries; the testicles and epididymis; the external genitals (glans penis, scrotum, clitoris, labia, and vagina); the prostate and the urinary bladder; the pancreas (especially its head); the kidneys; the intestinal mucosa; the thyroid; the bile-ducts (and gall-bladder); the liver; and the bronchi. The secondary growths are found especially in the lymph-glands, lungs, peritoneum, pleura, spleen, kidneys, and the osseous system.

Metastasis.—The malignancy of carcinoma is shown by its infiltrative local growth, whereby offshoots insinuate themselves in all directions into the substance of the parent tissue, choosing the regions of least resistance

¹ The term cancer is here used as synonymous with carcinoma and the German “Krebs.”

for its most pronounced growth. It is this faculty that makes the operative removal of these tumors so hopeless, for outside of the reach of the surgeon's knife there is usually an island of cancerous tissue which causes a recurrence after the excision.

Again, the function of colonization or metastasis reaches its highest degree in cancer, and adds the finishing touch to its malignant attributes. The transportation of the tumor-elements, by which remote secondary carcinomas are produced, is especially effected through the lymphatic channels. Very often the march of the new colonies can be traced by following the anatomic distribution of the lymphatics and their glands. The group of lymph-glands nearest the primary tumor interposes the first barrier, and itself becomes cancerous; from here new and more remote glands become

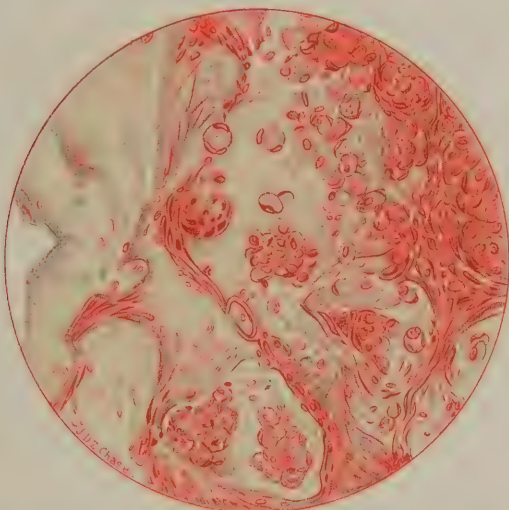


FIG. 71.—Cancer of the rectum. Mucoid degeneration in the stroma and epithelial cells. $\times 200$.

affected, and finally the viscera are reached. Much less frequently carcinoma uses the blood-vessels as routes for its metastases. This is generally brought about by the penetration, into a vessel, of a sprout of carcinomatous growth, forming a foreign body or a thrombus in the lumen of the vessel, from which minute particles or single cells are carried into the blood-stream as cancerous emboli, to lodge in other parts of the body. In this way it sometimes happens that an extraordinary number of these tumor-germs are sent into the circulation, producing an acute and widespread infection of other regions (acute carcinosis). It is not uncommon for these emboli to be detected in the capillaries on careful microscopic examination of such organs as the liver and lungs, even before they have reproduced extravascular growths. The destructive effect of such an ever-extending growth as carcinoma upon normal organs and tissues is readily comprehended. There is practically a substitution of a growing mass of foreign and functionally useless tissue for the normal structure; more than this, such a mass of cancerous growth is more easily subject to

degeneration, to necrosis, and to infection than the normal structures which it invades, and thus imperils them. Then, too, there is reason to believe that these abnormal growths have the capacity of elaborating their own harmful products (cytotoxins) as the result of their biologic activities, and that these products exert a baneful influence both upon the structures immediately surrounding the carcinoma and, by absorption, upon the body at large.

To say, however, that all carcinomas are functionally impotent is not correct; for there is an undoubted tendency for these neoplasms, when originating in certain important glandular organs, to partake, even if only in an imperfect manner, of the physiologic attributes of the parent tissue. Thus it appears that carcinomas of the adrenal, of the pancreas, and of the thyroid, even when extensive and for the most part displacing the normal glandular substance, do not cause in the victim those peculiar auto-intoxications which result from the destruction of these organs from other causes; from which we can only conclude that the elaboration of their peculiar products has been taken up by the cells of the invading new growth.

Parenchyma and Stroma.—When approached from the standpoint of its minute morphology, one feature of carcinoma stands out boldly: that is, it is a new growth composed of two essential parts—a *tumor-parenchyma* proper, and a supporting framework or *stroma*; one consisting of epithelial-like cells of various kinds and combinations, the other consisting mostly of a connective-tissue substance carrying within itself the vascular channels of the new growth.

Looking in general to the parenchyma of carcinoma, and in particular to the cells composing it, a very important question presents itself: Is there anything so peculiar in the morphology of the cancer-cell that it can be looked upon as a *specific element*? That is, is the cancer-cell to be distinguished morphologically from the normal epithelial cell, or from the epithelial cell in which other morbid processes are at work? This query has already been touched upon in the General Introduction to Tumors (page 161), and has been answered in the negative; here we shall repeat it and answer it similarly, though entering a little more into details.

Recalling again the assertion that many carcinomas resemble in their morphology such fibro-epithelial neoplasms as papilloma and adenoma, and extending this likeness to the constituent cellular elements, as may in all propriety be done, we can comprehend that there are carcinomatous cells which resemble ordinary epithelial cells so closely that no morphologic analysis which our present facilities for examination afford enables us to say that the individual cell came from a normal epithelial structure, from an adenoma, or from a carcinoma. Which is to say, in other words, that those cancers most closely approaching the morphology of typical neoplasms show no specific cellular features. However, in many rapidly growing cancers the constituent cells show alterations which, if not peculiar to these tumors alone, are nevertheless most conspicuous in them. The cell may often attain a size which is rarely reached by other morbid epithelial cells. Its protoplasm may show changes in the disposition of the cytoplasmic reticulum and in the cytoplasmic granules. Its protoplasm may be vacuolated to a pronounced degree, or it may contain certain peculiar spheric or ovoid bodies with special affinity for certain dyes, or it may contain masses of pigmented, hyaline, colloid, keratogenic, or glycogenic material; and other inclusions,

like engulfed neighboring cancer-cells, or leukocytes, or foreign débris, may also be found. We have already seen that the cells of sarcoma exhibit many of these peculiarities. Turning to the nucleus, the most marked anomalies are found. Nuclei excessively large are seen, sometimes beside those below the usual size. The chromatin may be scanty (hypochromatosis) or excessive (hyperchromatosis), and it may be arranged in a loose mesh-work or aggregated in a compact mass. Nucleoli are single or multiple and sometimes excessively large. As in the case of sarcoma, the nucleoli and chromatin reticulum of the nucleus exhibit a marked dichromophilism, but this is in no way specific for carcinoma.

The figures produced by nuclear division in carcinoma show all the various abnormal types to which reference has already been made. Irregular and pluripolar mitotic figures have been looked upon as especially significant of cells of carcinomatous origin; and though they are occasionally seen in epithelial cells engaged in rapid regeneration or under the influence of certain infections, they certainly furnish the most important diagnostic element in determining the nature of a neoplasm from its cells alone. With ever-improving methods and with further search, it may be that some cytologic feature will be discovered which will stamp the carcinomatous cell as an individualistic morbid element.

But it is only by the grouping of the constituent cells, and by the relation of these cellular colonies to their stroma, and the relation of the whole newly formed tissue to its environment, that carcinoma can positively be differentiated. To this subject of cell disposition we shall refer in more detail when considering the separate varieties of carcinoma.

The stroma in which the carcinomatous cell groups are disposed is usually a more or less perfect connective tissue, sometimes closely resembling that seen in nonmalignant fibro-epithelial tumors, and again exhibiting certain distinctive features. There is a wide variation in the stage of organization reached by the stroma in different carcinomas and in different parts of the same tumor. A richly cellular growth, with scanty development of intercellular fibrils resembling embryonic connective tissue or that seen in regeneration of this tissue, is found with particular frequency in the rapidly growing neoplasms. In other instances the organization is more perfect, the stromatic cells becoming spindle-shaped with more and more intercellular substance, reaching finally a stage in which dense connective tissue with quiescent cells is found between the islands of cancer-cells. As naturally would be supposed, the softer neoplasms are those with poorly developed stroma.

Along with the proper connective cells, the stroma of carcinoma often contains other elements. Many foci of embryonic mesodermic cells or lymphoid cells are found, making the familiar "round-celled infiltration" of these tumors. Leukocytes, both the polymorphonuclear and mononuclear forms, are seen in the tumor-framework; and the different tinctorial varieties of the white blood-cell—the neutrophile, acidophile, and basophile—are represented. Plasma-cells, often in large numbers, appear in the tumor-stroma, marking inflammatory reactions; and mast-cells sometimes appear, especially at the growing borders of the tumor, where retrogressive changes are going on in the matrix. Occasionally giant cells are seen in the stroma, apparently in the act of phagocytosis; and various foreign substances, like cholesterol crystals and detritus, are found in them. Bodies

with unusual staining reactions are also at times present, of a class represented by the peculiar spheric fuchsinophilous granules described as "Russell's fuchsin bodies." Bacteria, and perhaps yeast organisms, are to be found; and in rare cases in which a tuberculous infection is implanted upon a cancer, tubercles are encountered in the stroma, along with their bacilli.

Both blood-channels and lymphatic channels abound in the stroma, which thus serves as the carrier of these structures; the number and disposition of these nutrient canals vary in different tumors.

A very important peculiarity of carcinoma is *its ability to utilize surrounding tissue-elements as a supporting framework for its own cells*. Invading a part in which connective tissue pre-exists, the groups of cancer-cells simply utilize this tissue as a stroma; and what happens in the case of connective tissue also occurs in other structures. For instance, the cells of fatty tissue or the fibers of striated or nonstriated muscle may be called upon to furnish the cancerous framework; and, especially in the case of metastatic growths, the adenoid cells and reticulum of lymph-glands or the columns of liver-cells may supply the supporting framework for the new growth. For the most part the nuclei of the stroma show amitotic division, but it is also possible to discover various figures of mitotic division here.

Retrogressive Changes.—Evidences of degeneration are not uncommon in the cancerous stroma. A fatty metamorphosis is sometimes seen and may affect wide areas of the growth. A hyaline transformation is also possible, the transformed stroma taking on a homogeneous, glassy, swollen aspect, while its cells become indistinct. Closely allied to the preceding are the mucoid, colloid, and gelatinous degenerations in the stroma, and in rare instances the altered stroma has been found to give an amyloid reaction. Calcification, even in carcinoma having no connection with bones, is observed, the calcareous material being mostly deposited in the form of concentric masses, though cases have been noted in which a general deposit of lime salts took place at the periphery of a carcinoma, making a sort of calcareous capsule for the tumor.

Certain of these degenerations affect both the tumor-parenchyma and the stroma; at other times only one of the basic structures becomes involved. Several varieties of carcinoma have been established on this ground. That variety in which the stroma has taken on abundant growth to an advanced stage, resulting in the contraction and even death of certain groups of carcinomatous cells, and producing a growth often of stony hardness, is the "scirrhus cancer." A richness in cells, as has before been noted, together with a scanty or loose-meshed and usually abundantly cellular stroma, characterizes the "medullary" or "encephaloid" cancer. A colloid or gelatinous degeneration of the parenchyma, with or without a similar change in the stroma, producing a growth in which the tumor-elements are surrounded by a mass of the foreign material, makes the "colloid cancer," and similarly a mucoid transformation would give rise to the growth designated as "myxomatous cancer." Hyaline metamorphosis of either or both the parenchyma and stroma, upon becoming extensive, makes a growth resembling the cylindromatous sarcoma, and is therefore styled "cylindromatous" carcinoma.

Histogenesis.—Turning our attention now to the question of the histogenesis of carcinoma, we are largely prepared, from what has preceded, to ignore the older theories which ascribed the origin of the tumor-elements to a

metaplasia of connective-tissue cells,¹ and to accept the doctrine propounded a quarter of a century ago by Thiersch and Waldeyer, that *cancer-cells originate in altered pre-existing epithelial cells*. Numerous observations have settled this point, apparently beyond dispute, especially the studies upon young carcinomas in various localities. In the skin, for example, a direct continuity may be traced between the carcinomatous foci and the sprouts of pavement epithelium, which in the diseased area plunge more deeply into the underlying connective tissue than is normal. At some particular point the pavement epithelial cells assume an undue activity, multiplying rapidly and producing cell groups which push their way into the regions beneath. That the cells found in cutaneous cancers originate from those of the pavement epithelium is clearly shown by their retention of many of the biologic characteristics of the parent tissue; for they take the shape and general appearance of the mother-cells, often reproduce such structures as the protoplasmic bridges of epithelial prickle-cells, and undergo various keratogenous changes seen in their progenitors. In the same way, cancers of the stomach and intestine reproduce the cylindric epithelium of the original surface or glandular epithelium; those in the bronchi spring from the cylindric cells of the mucosa, in the lungs from the flat cells lining the alveoli, and in the liver from the original liver-cells. The direct transformation of the normal to the abnormal elements has been repeatedly witnessed by competent observers. There are, however, some apparent contradictions to these views of carcinomatous histogenesis, as seen in the case of flat-celled neoplasms originating in the digestive mucosa, in which only cylindric cells normally are found; but the phenomenon is explained by assuming a metaplasia of the normal epithelial elements preceding the growth of the carcinoma, an assumption strengthened by the evidences of a similar metaplasia under other conditions. For those rare instances in which a primary carcinoma begins in a purely mesodermic structure, like bone, a previous embryonic misplacement of epithelial elements seems the only satisfactory explanation.

The conduct of the connective tissue which becomes the stroma of the beginning carcinoma is not always easily followed. Whether an activity and proliferation of its cells precede or succeed the primary epithelial growth is a question upon which opinions differ. It is held on one side that the connective-tissue elements first arouse into activity, sending wandering cells between the epithelial cells of a given part, by which these latter elements become separated from their original continuity and then begin to exhibit those increased and peculiar proliferative properties common to carcinoma-cells. A great deal of weight is laid upon this severance of the epithelial cell from its natural abode, as a potent factor in the histogenesis of carcinoma, though it is evident that the cell must contain within itself a capacity for reproducing carcinomatous offspring, else any epithelial cell or group of cells thrown out of normal surroundings by such factors as mal-development or traumatism might make a cancer, which of course is not the case. So far as the participation of connective-tissue proliferation is concerned, it may be, as has been claimed, that its activity and growth are a prominent factor in the histogenesis of some carcinomas; but in other instances

¹ In this connection it must, however, be recalled that the opinions of embryologists concerning the immutability of the germ-layers are not so positive as formerly; and that certain experimental pathologists claim that a metaplasia of epithelium into connective tissue can occur. If this be true, the converse also may be possible—that is, metaplasia of connective tissue into epithelium.

it seems to play a decidedly secondary part, not assuming noticeable proportions until the epithelial growth has attained a considerable extent; and finally it is in point to recall those cases in which the growing carcinoma appropriates for its stroma other elements besides connective tissue.

Etiology.—Turning first to the patient, we are met with the fact that cancer is pre-eminently the malignant neoplasm of advanced life. Statistics gathered with great care from large numbers of cases show that 70 per cent. of these neoplasms appear between the fortieth and seventieth years of life, and that below the fifteenth year the disease is practically unknown.

There must be something, then, in the environment afforded by the tissues of advanced life that makes an especially suitable soil for cancer, or there must be at this time in life an action of causes not operative earlier. As to the causes themselves, we must distinguish sharply the predisposing from the exciting factors. Of the first we know considerable from clinical statistics, but of the latter we are still much in the dark.

The theory of embryonic misplacement, once vigorously espoused in connection with carcinoma, now finds little support. The characteristic tendency of cancer to start as a primary growth in such localities as the lips, nipples, anus, and uterine neck, where mucous and cutaneous surfaces or flat-celled and cylindric-celled surfaces adjoin, was held in support of the embryonic hypothesis; for here, it was argued, where germ-layers once met, misplacement of rudimentary tissue-germs would be especially liable to occur. But it may properly be asked why *carcinoma* should be the favorite neoplasm to appear in these situations, and again it must not be forgotten that these same localities are especially exposed to traumatism and to infection.

Irritation, both immediate and continued, has a profound influence in determining the localization of carcinoma, unless all clinical evidence on this head be set aside. A trustworthy history of traumatism in the site selected by the primary carcinoma has been obtained in a fair percentage of cases. The origin of these malignant growths in scars resulting from traumatism or from ulceration bears on this point. Chronic irritation, doubtless for the most part of an inflammatory character, predisposes to carcinoma in individuals reaching the cancer period of life, as shown in the appearance of these growths in the gall-bladder or bile-ducts in cases of biliary calculus and accompanying chronic inflammation. The origin of carcinoma in mammary glands once the seat of mastitis is to be similarly interpreted, as is also the case when the disease appears in the cervix of a uterus long subject to irritating discharge and slow inflammation. The notorious predilection of cancer for the lips and tongue of tobacco and alcohol users can likewise be charged to previous irritation. In many of these cases there is, at the commencement of the irritation, an infection of the site from which the cancer starts, and the inflammation is due to the continued action of infectious organisms and their toxic products. This tendency for certain infections to prepare a soil for carcinoma is well shown in the cases in which the disease arises in connection with lupus, and probably also where cancer originates in partly healed gastric ulcers. In all of these instances, however, only one factor in the causation of the neoplasm has been considered; otherwise there would be no accounting for the well-known facts that, after all, comparatively few of these seats of irritation become cancerous, and that this disease frequently originates where there is no evidence of previous irritation. There must be a *specific exciting factor* among the primary causative

influences; and here we reach the realm where speculation begins and is most prolific.

The problem of the etiology of carcinoma is very much like that pertaining to sarcoma; and at the present time the *parasitic theory* of its etiology claims the greatest share of attention, though it meets with opposition from some of the most accomplished students of this subject. Both in the discussion of the etiology of tumors in general and in connection with sarcoma, the points in favor of the parasitic theory were mentioned, and they apply to carcinoma as well. Granting the existence of a minute animal or vegetable parasite which invades certain epithelial cells and incites them to the abnormal proliferative activity resulting in the cancerous neoplasm, many aspects of the problems concerning these tumors are made clear, though there now seem to be insurmountable obstacles in other directions. The appearance of cancer at the various orifices of the body and in localities subjected to traumatism and to irritation of various kinds would support the parasitic theory, for in all of these places especially favorable openings for infection or soils with lowered resistance would be offered. The carrying over of the specific parasite in the transported cells would make more easy the explanation of carcinomatous metastases. That parasites do exist in carcinomatous tumors no one can deny, and that representatives of bacteria and yeast fungi have been here found is unquestionable. But to prove the specific causative relationship of any of these microscopic species is quite another matter, and certainly has not been accomplished at the present time. On the other hand, we find the views of distinguished investigators who attempt to explain the etiology of carcinoma on other grounds to be entirely out of accord with each other, and it must therefore be said that at present this important problem is still unsolved.

Varieties of Carcinoma.—The subdivision of carcinoma seems to be best accomplished on purely histogenetic grounds, and accordingly it is appropriate to classify the varieties into (a) the pavement-celled, (b) the cylindric-celled, and (c) the glandular.

Pavement-celled Carcinoma.—Flat or pavement-celled carcinoma originates, for the most part, from similar cells lining the cutaneous or mucous surfaces of the body. The quite familiar neoplasm growing from the lip, and often styled an *epithelioma*, represents the type of these tumors. They begin as undefined infiltrations or thickenings of a part, and may grow beneath the surface for considerable areas, or spring above the surface in the form of nodular or wart-like growths, sometimes taking a villous or cauliflower-like appearance. They are generally more firm than cancers growing within the body cavities or organs, and some of them become very dense and horn-like. Necrosis of the central portion of the growth may set in early, producing ulcerating cancers.

Depending upon the shape assumed by the tumor-mass, neoplasms of this class have been described as “warty” cancers, “villous” cancers, and “horny” cancers.

This variety of carcinoma may appear in the skin of any region of the body, but chooses with especial frequency the various orifices, like the lips, nostrils, eyelids, prepuce, vulva; and in the pavement-celled mucous membranes it may also appear, selecting especially the tongue, esophagus, larynx, vagina, and vaginal portion of the uterus.

The microscopic anatomy of these cancers exhibits a tumor-parenchyma

composed of flat, round, or polygonal cells, varying in size and arranged in groups or alveoli, surrounded by a stroma more or less rich in cells. In the newly developing portions of the growth the parenchymatous cells are mostly round and undifferentiated, while the stroma is abundantly cellular with an imperfect development of fibers. In more advanced portions the epithelial cells tend to become flattened and to exhibit various metamorphoses like the keratogenous or horny changes to which pavement epithelium is subject. Here the alveoli become much larger, and in the central portions marked degenerative changes, even resulting in death of the cancer-cells, may be seen, while at the periphery young cells occur with evidences of nuclear activity in the shape of regular or irregular forms of mitosis. There is no uniformity in the shape assumed by the colonies of cancer-cells; in the newer portions of the growth they tend to advance in straight lines, several cells lying side by side, following in regular order those in advance, and invading the lymph-spaces of the tissue; while in the older groups a central area can be seen, from which offshoots extend in all directions, often anastomosing freely with other groups. The histogenetic impress of pavement epithelium is marked in various ways upon the older portions of the cancer-parenchyma, and shows with especial prominence in the frequent reproduction of the intercellular protoplasmic bridges or "prickles" which pass through the cement-substance between the cells, making a very perfect picture of the "prickle-cells" as seen in normal surface epithelium. Eleidin and keratin granules also appear in the more mature cells, and a peculiarity of many of these superficial cancers is the production of concentric whorls of cells more or less advanced in horny changes and exhibiting a repugnance to nuclear stains, constituting the so-called "epithelial pearls" or "birds' nests" of flat-celled cancer. In these concentric bodies may be found some of the most marked evidences of nuclear and protoplasmic necrosis in various stages, together with the peculiar process of inclusion of one epithelial cell by another, and an active invasion of leukocytes, some of which are degenerated and others apparently engaged as scavengers to devour the detritus resulting from necrotic processes.

In the older portions of these tumors the stroma may attain a coarsely fibrous character like old scar-tissue, thus becoming an important element in producing the dense and hard flat-celled carcinoma. In other growths, or in certain regions in a single tumor, the stroma is more cellular and the fibrils less numerous, until a condition like that of embryonic or regenerating connective tissue appears. Scattered in various localities in the stroma, foci of small-celled infiltration are found, and, especially about the growing edge of the neoplasm, collections of plasma-cells and mast-cells appear.

Cylindric-celled Carcinoma.—These neoplasms may arise either from the cylindric cells covering such mucous surfaces as the digestive tract and respiratory passages, or preferably from the cells lining tubular glands like those in the intestine, and from the ducts of acinous glands like those of the mamma, which are lined with cylindric cells. They are most often found in the stomach (forming a portion of the gastric carcinomas), the intestines, rectum, bile-ducts, and uterus, and begin as localized infiltrations, rapidly involving the structures lying beneath the mucosa, frequently ulcerating in their central portions. For the most part, the tumors are soft and they tend to degenerate, especially in the direction of colloid and mucoid meta-

morphoses. Growing from a free surface, they often produce papillary or villous neoplasms.

The parenchyma of these carcinomas shows the cylindric cells, generally closely resembling those normally encountered, arranged in lines of growth that produce more or less perfect tubules. That is to say, the cells, several layers deep, arrange themselves around a central space, and in some portions of the new growth the resemblance to normal tubules may be quite perfect. As the tumor advances, however, the normal limits of tubular growth are disregarded and the cylindric-celled tubular sprouts extend in all directions, while the excessive proliferation of their cells may alter the shape of the original lumen of the tubule or even close it entirely. In

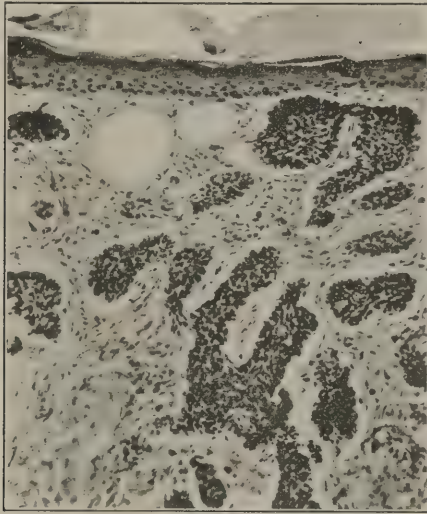


FIG. 72.—Tubular carcinoma from the forehead. $\times 150$. (Dr. Montgomery's case. Dr. Rickett's preparation.)

rapidly growing tumors, many of the cells composing the abnormal tubules contain nuclei in the process of mitosis.

The stroma of cylindric-celled carcinoma is generally more cellular in well-developed portions of the tumor than is the case in flat-celled cancer, and this cellular connective tissue is more regularly disposed about the parenchymatous elements. In studying these neoplasms, especially from a diagnostic point of view, it is important to note the relative position of the proliferating tubules. When these are found growing into and beneath the muscularis mucosa in the intestine and stomach, for instance, no doubt need be entertained as to the nature of the neoplasm (Ribbert).

Glandular Carcinoma.—This takes its origin from the glandular epithelium of such organs as the mamma, pancreas, liver, thyroid, salivary glands, kidneys, prostate, testicle, and ovaries. Like the preceding group, the glandular carcinomas begin as infiltrative growths in the parent tissue, and for the most part produce rather soft tumors. The histogenesis of these cancers and their microscopic morphology are such as to produce a more or less

marked resemblance to the original glandular structure; hence the propriety of the term *adenocarcinoma*, often applied to them. In the discussion of the fibro-epithelial tumor known as adenoma, attention was invited to the occasional difficulty of drawing a sharp line between the benign and the cancerous glandular growths. The macroscopic details upon which this differentiation depends are mainly the infiltrative and lawless tendencies of the primary cancerous growth, features which are strongly emphasized by its minute anatomy.

Histologically the glandular carcinoma exhibits a parenchyma composed of polymorphous cells arranged in alveoli which often anastomose widely and are separated by a connective-tissue stroma. The type of this sub-variety is seen in the cancer of the breast arising from the lacteal glands. The polymorphism of the epithelial cells is well shown in specimens

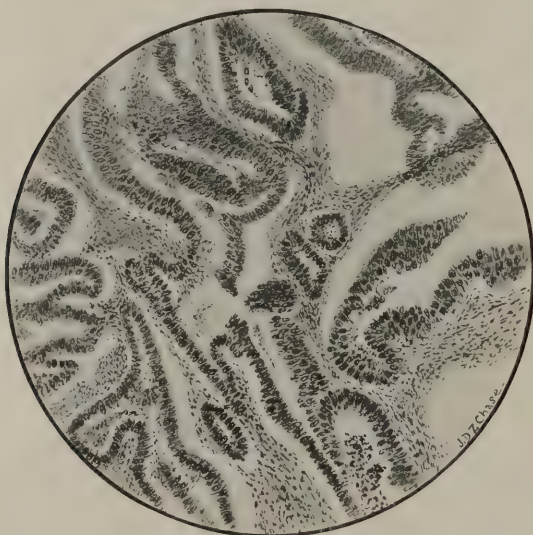


FIG. 73.—Adenocarcinoma of the rectum. $\times 65$.

obtained by scraping the tumor-surface and freshly examined. Their nuclei are usually well developed and often multiple, producing carcinomatous giant cells; karyokinetic figures, both of normal and abnormal types, are abundant in the soft and rapidly growing examples, and inclusions appear frequently. A common alteration of the parenchymatous cells is fatty degeneration. The alveoli vary widely in their size and in the grouping of the cells, but the predominant characteristic which serves as the most important diagnostic point is the atypical arrangement of the cell groups of the alveoli as compared with the normal gland and with simple adenoma. The lumen of the normal gland is generally lost, and the absence of the *membrana propria* and of the normal ducts is an important diagnostic feature.

The stroma of these tumors shows the usual variations common to other cancers.

PLACENTOMA.

Within the last few years we have specific knowledge of a peculiar kind of tumor which has so unusual an origin and exhibits such a distinctive morphology and physiology that it can only be considered separately. It is a *malignant neoplasm* in the fullest sense of the word, exhibiting the morbid physiologic characteristics of sarcoma or carcinoma.

No doubt, before its individuality was discovered, it was confounded with uterine sarcoma or carcinoma, and, even since it has been recognized, a great deal of doubt has been entertained as to its origin, as shown with great clearness in the various terms which have been employed to describe it, as, for instance : *Deciduoma* and *Deciduoma malignum*, *Sarcoma choriondeciduocellulare*, *Sarcoma chorii*, *Sarcoma choriocellulare*, *Choriocarcinoma*, *Carcinoma syncytiale*, *Epithelioma seriotinale*, and *Syncytioma malignum*. It is evident that this terminology refers mostly to the ideas which have been held concerning the histogenesis of these tumors, and this applies to the term *Placentoma* here adopted, which is at least noncommittal to certain of the theories.

Placentoma has been found primarily in the cavity of the uterus and the Fallopian tubes, but not in ovarian and abdominal pregnancies. Here it springs from the placental site (*decidua serotina*), either during the course of a uterine or tubal pregnancy or after the termination of this pregnancy (at term or prematurely), from placental remnants at the site of the decidua serotina. It is notable that placentomas follow not only apparently normal gestation, but with especial frequency (about one-half of the cases) such an abnormal form as mole-pregnancy. More remarkable still are the cases reported by Schmorl and by Harris, in which no primary neoplasm was found in the uterus or Fallopian tubes, but in a distant organ like the kidney.

The tumors grow as soft, spongy, villous, bleeding masses of varying size, sometimes single and again as multiple nodules springing from the chosen area. In appearance they are not unlike portions of placenta, and detached pieces removed from the uterus have several times been at first mistaken for retained placenta. They generally grow with great rapidity, causing the uterus to increase in size quickly and progressively, while, from their highly developed blood-supply and fragile consistency, hemorrhages often accompany their progress. They have no respect for adjacent tissues, and invade the uterine wall much as a carcinoma would. More than this, they are capable of producing metastatic growths which appear in such regions as the vagina, labia, lungs, kidneys, gall-bladder, thyroid, intestines, and even in the brain. The secondary nodules resemble placenta, and are generally not large. They may be very numerous in the lungs, giving an appearance like disseminated miliary tubercles.

The clinical picture which placentoma produces is briefly as follows : After the termination of a full-term pregnancy, after an abortion, or after the expulsion of a mole, generally with a very short interval, uterine hemorrhage starts afresh, while at the same time the uterus begins to swell. From the loss of blood, and doubtless also from the intoxication peculiar to malignant tumors, the patient rapidly becomes anemic and develops a peculiar cachexia. Shreds and pieces of the new growth may be passed from the uterus, and an examination reveals the spongy, friable mass filling the uterine cavity. Secondary tumors soon appear, their presence being visible when they attack

the vagina or labia, or shown by physical signs and the spitting of blood when the lungs are invaded. After a very short time (three to nine months) the patient succumbs to the devastating disease. In the cases with no uterine tumor, persistent nausea and rapid decline have been noted.

The histology of placentoma is characteristic, and its peculiar features have been plainly shown by Marchand, to whom our present knowledge upon this point and upon histogenesis is mostly due. The tumor is made up of *parenchyma alone*, the absence of a newly formed integral *stroma* being one of its histologic characteristics; which, while very striking, is not confined to this neoplasm alone, as we have seen in the description of carcinoma (page 208), which sometimes utilizes as a framework the structures in which it grows. The parenchyma consists of two chief portions: an extensive



FIG. 74.—Section from primary uterine tumor, showing its alveolar structure with the cavities filled with blood; $\times 60$ (Williams).

protoplasmic ground-substance, *syncytium* or plasmodium, usually arranging itself into a sort of network to produce an alveolar structure, and of numerous small polyhedral cells, which group themselves in the alveoli provided by the peculiar disposition of the plasmodium. In the most typical form of placentoma there is no evidence of a subdivision of the plasmodial network into separate cells, though it contains numerous nuclei; but in other cases the protoplasmic network does divide into irregular nucleated masses, into giant cells, and into immense epithelioid cells with large nuclei richly endowed with chromatin. Vacuoles are often abundant in the syncytial tissue, and it not infrequently shows evidence of hyaline metamorphosis. The smaller, polyhedral, generally mononuclear cells are remarkable for the frequency with which they show glycogen granules. Along with these two chief parenchymatous elements, the tumor-substance contains abundant blood-sinuses with areas of free hemorrhage, and detached masses of syncytium or syncytial cells are often found floating in the blood-sinuses. As a result of

these hemorrhages, a copious deposit of blood-pigment, especially in phagocytic cells in and around the tumor-parenchyma, can be seen.

As to the origin of the tumor-parenchyma, much discussion has been aroused, it being commonly held, prior to Marchand's studies, that the elements were of a decidual nature—that is, were developed from the decidual cells of the maternal decidua, these being originally of connective-tissue birth; hence the term “sarcoma,” applied to these growths. Marchand's views, now commonly accepted, are that the tumor-parenchyma originates exclusively from the two epithelial layers covering the chorionic villi which project into the maternal decidua at the site of the placenta (*decidua serotina*). Of these two epithelial coverings of the chorionic villi, the external one (*syncytium*) is supposed to be of uterine origin from the epithelium of the uterine or tubal mucosa (and glands), and furnishes the plasmodium of the syncytial neoplasm; while the inner layer (Langhans's layer) is of fetal origin (ectodermic cells), and furnishes the small polyhedral cells contained in the alveoli of the placentoma or syncytioma.¹

The transportation of the tumor-elements by which the secondary growths are produced is effected almost entirely through the venous channels, either through the parenchymatous elements (especially the plasmodial masses) of the primary tumor breaking (or eroding) into a blood-vessel, or through the detached particles floating in the blood-sinuses. The lymph-spaces of the uterine wall are not infrequently invaded by the tumor-cells, but the rarity with which the pelvic lymph-glands are infected speaks against the spread of the neoplasm through these channels. Thrombi containing syncytial masses are especially frequent in the pulmonary blood-vessels; and parietal lodgement and penetration of the vessel-wall may be seen, though whether this is due to the ameboid movement of the plasmodium or to its digestive action (which, like certain carcinomatous cell groups, or like the implanted impregnated ovum, it seems to possess), or to both, is not fully determined.

As to the etiology of these neoplasms of so remarkable an origin, nothing whatever is known.

TERATOMA.

It remains for us briefly to consider still another class of new growths which stand in close relation to several varieties of the tumors already discussed. These are the *teratomas*, a group of neoplasms containing heterogeneous tissue-elements usually so far advanced in development as plainly to resemble some one or more of the mature tissues or organs, either in macroscopic or microscopic morphology or both. The dermal structures in one kind of teratoma (*dermoid*) plainly recall the skin and its component parts, while skin, muscle, cartilage, bone, intestines, certain viscera, nervous tissue and the like are reproduced in the more complicated teratomas with more or less anatomic fidelity. Sometimes the reproduction is so complete that the teratoid tumors contain plainly recognizable fetal parts, the confines of that

¹ Whether the syncytium is really of maternal or fetal derivation can scarcely be regarded as settled at the present time, but in either case there seems to be no doubt as to its *epithelial nature*; and, with the ectodermic nature of the other elements of the placentomatous parenchyma proved, there can be no doubt as to the epithelial affinities of this neoplasm. Therefore, if there is any propriety at all in attempting to classify it with other tumors, it most naturally falls in with carcinoma.

group of pathologic anomalies known as congenital malformations being reached. Indeed, it seems that teratoma serves to bridge the gap between a number of what we are pleased to style "true" tumors and the malformations only to be ascribed to errors of embryonic or fetal development, and for this reason the embryonic theory of tumor-genesis here obtains important support.

Usually these teratoid growths are not large, though examples weighing twenty or thirty pounds have been recorded. As a rule, the tumor-mass is not characteristic in appearance, but at times even the external configuration recalls some imperfectly formed bodily part. Cystic metamorphosis, as has already been remarked, is extremely common, and these generally epithelial-clad cavities contain fluid (clear or cloudy), gelatinous, mucoid, fatty, grumous, or calcareous material. A soft, wax-like substance, white or yellowish, containing cholesterin crystals, exfoliated epithelial cells and scales, and hairs, is frequently found, more especially in the so-called "dermoids" of the ovaries. Teeth, more or less perfect, and nails are quite common objects in the walls of dermoids; and skull-bones, separate or united in anatomic relationship, imperfect limbs, eyes, brains, bowels, etc., have all been recognized at times, the latter three for the most part only on microscopic section. It is here noteworthy that Wilms found nervous tissues in traces or larger amounts in ordinary ovarian dermoids, and it is highly probable that similar careful histologic analysis in all teratomas will reveal a more complex organization than is at first apparent. Thorough microscopic study should be made not only of tumors whose teratoid structure is clear, but also of those neoplasms in which anomalous tissues appear as muscle in the kidneys or testicles, cartilage in the mammary glands, and so on, since these growths seem only ascribable to embryonic aberrations and often show more structural complexity than would be suspected from a superficial examination.

The ovaries are the favorite point of origin of teratomas, the testicles being less often involved. Outside of the genital glands, teratoid growths may spring from the abdominal cavity, from behind the peritoneum, in the kidneys, the mammary glands, parotid gland, about the eyeball, in the neck especially at the points where the gill-clefts once existed, and in the brain; that is to say, in situations where important embryonic foldings occurred. Many cutaneous cysts (like the so-called "atheromatous cysts") are of a teratoid nature, though they also may start from postnatal causes, like traumatism and operative procedures, which produce mechanic transplantation of cutaneous structures.

Most teratomas grow slowly, but some of them increase rapidly in size, even rivalling sarcoma and carcinoma; and these rapidly growing teratoid neoplasms show other evidences of malignancy, like spreading along contiguous surfaces, recurrence after removal, and even by metastasis, whereby new tumors, with a portion or all the structural complexity of the original, spring into existence in remote localities. We see, therefore, that even in this class of tumors, whose embryonic origin is usually so easily demonstrable, the same morphologic and functional characteristics of tumors proper exist.

As to the period of life in which these tumors occur, it is really strange to find an exception to their appearance as congenital growths, though this is occasionally the case, for teratoma has been found to begin its growth even in adults. Here we have another argument for Cohnheim's embryonal

theory, holding that tumors arise from misplaced embryonic rudiments, which may remain latent for years.

It will be inappropriate to discuss here all the theories advanced to account for this group of new growths. The perfect teratomas which reproduce fetal parts most faithfully must be regarded as instances of fetal inclusion (the *fœtus in fœtu* of Meckel); and in their production such factors are probably concerned as accidents to the ovum in its early segmentations (demonstrated as worthy of consideration by modern experimental teratology), or subsequent faulty fissions in the young embryo. The included embryo or embryonic part must remain dormant in those cases in which complex teratoid growths appear after birth, a condition difficult to comprehend. Probably in the less complex teratomas, a pinching-off of tissue-rudiments, such as Klebs suggests, is what actually happens during development to furnish the teratoid nidus.

PATHOGENIC MICROPARASITES.¹

INTRODUCTION AND GENERAL MICROPARASITOLOGY.

In its whole aspect, pathology has been changed in the quarter-century now ending. This change, which is sufficiently far-reaching to be termed a revolution, is to be ascribed to the discovery of the pathogenic microparasites and of their intimate relationship to disease. The description of many morbid processes has been entirely rewritten in this period, which, from the marvellous progress made, must be regarded as one of the great epochs in human advancement. Light has been thrown on many of the obscure problems in pathology, and there is daily evidence of further achievement in this new field. So that now, to understand the nature of many a given disease, the student must be familiar not only with its morbid anatomy and

¹ Since it is now customary to present the subject of bacteriology in the medical curriculum as a course separate from and usually preceding pathology, it seems superfluous to go into elementary descriptive details in this section of a text-book on pathology or to encumber it with technic minutiae. More profit appears attainable by assuming that the student, in approaching this topic, comes with a theoretic and practical knowledge of elementary bacteriology. For those who take up this section without the preliminary knowledge just indicated, a study of one of the standard text-books on bacteriology now readily accessible is advised, either as a preparatory course or as a supplement to the various topics here presented. Laboratory practice is, however, indispensable; it alone gives tangibility to the knowledge of parasitology gained from a study of such text-books and of this article.

Having particularly in mind the needs of the student, it has been thought wise not to encumber this section with bibliographic references. Those who would seek the original sources of information should consult the special journals devoted to parasitology, such as the *Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten*, *Archiv für Hygiene, Zeitschrift für Hygiene und Infektionskrankheiten*, *Annales de l'Institut Pasteur, Hygienische Rundschau, Arbeiten aus dem kaiserlichen Gesundheitsamte*; and those dealing with pathology and bacteriology, such as *Virchow's Archiv, Centralblatt für allgemeine Pathologie und pathologische Anatomie, Beiträge zur allgemeinen Pathologie und zur pathologischen Anatomie, Archives de Médecine expérimentale et d'Anatomie pathologique, Journal of Pathology and Bacteriology, and Journal of Experimental Medicine*. For studying the literature, besides the general indices, such reviews as *Baumgarten's Jahresbericht über die Fortschritte in der Lehre von der pathogenen Mikroorganismen*, and the *Ergebnisse der allgemeinen Pathologie und der pathologischen Anatomie* of Lubarsch and Ostertag are especially valuable.

Among the manuals and text-books, Flügge's *Die Mikroorganismen* on general bacteriology, Migula's *System der Bakterien* and Fischer's *Vorlesungen über Bakterien* on the systematic side, are rich in information, and the first two provide extensive bibliographies.

Bacteriology as applied to clinical studies is best represented by Heim's *Lehrbuch der Bakteriologischen Untersuchung und Diagnostik*, and by Levy and Klemperer's *Clinical Bacteriology*. Mention must also be made of Duclaux's *Traité de Microbiologie*; the section on Parasitic Fission-fungi, Yeasts, Moulds, in Ziegler's *Lehrbuch der allgemeinen Pathologie und pathologischen Anatomie*; the sections on Infection and Pathogenic Microbes by Charrin, Charrin and Hugounenq, and by Roux in *Bouchard's Traité de Pathologie Générale*; and Flexner's article on Micro-organisms in the *Twentieth Century Practice of Medicine*. Gautier's *Les Toxines Microbiennes et Animales*, and Vaughan and Novy's *Plasmains and Leukomains* deal especially with the chemistry of the poisonous bacterial products. Among the more general and elementary works are Lehmann and Neumann's *Bakteriologische Diagnostik*, Abel's *Taschenbuch für den bakteriologischen Praktikanten*, Abbott's *Principles of Bacteriology*, Schürmayer's *Pathogene Spaltpilze*, Sternberg's *Text-book of Bacteriology*, McFarland's *Text-book upon Pathogenic Bacteria*, and Günther's *Bakteriologie*.

its morbid histology, but also with its parasitology. How essential this knowledge is may be appreciated when it is known that the morphologic pictures recognized as diseased conditions of organs and tissues, and the physiologic consequences recognized clinically as symptoms of disease, may all be primarily charged to the presence and activity of microscopic parasites. Tuberculosis, for example, is not only that disease in which conglomerations of tubercles, cheesy masses, and cavities appear in various organs, or that disease in which the microscope defines the elements of the individual tubercle; but it is all of this, plus something more—that is, the micro-organism of tuberculosis, which we now believe to be the cause of the disease.

Parasitism in its gross forms was long ago recognized, both in the animal and the vegetable kingdoms; and it was likewise known that certain parasites of animals and plants proved detrimental to their hosts, and that this harmful influence might even cause the death of the host. Long before the era of bacteriology it had been determined that certain animal organisms were parasitic in man, and several grave or even fatal human maladies, as those produced by the tapeworms, especially the echinococcus, and by the guinea-worm, were traced directly to their presence. Among the Arachnidæ the itch-mite has historic notoriety. And even microscopic parasites were not unknown before the beginning of bacteriologic science, as is shown in the case of the *Trichina spiralis*. That a world of organisms, microscopic in size and deadly in effect, lay hidden in the organs and tissues of numerous morbid affections in man was scarcely dreamed of until the perfection of the microscope, the improvement of technic, and the application of modern methods of biologic inquiry to the study of human diseases opened the way to the new knowledge relating to microscopic animal and vegetable parasites. With these microparasites and their disease-producing tendencies in the human flesh we shall now concern ourselves.

The inhabitants of this microbiologic world are occupied in many of Nature's phenomena, of which disease in animals and plants is but one. A large variety of the representatives of plant life, especially the great group known as bacteria, are important agents in fermentation, putrefaction, and decay, assimilation and growth of higher plants, etc., and some of the lowly animal micro-organisms are similarly engaged in extrinsic work, both constituting the *saprophytic* organisms, so called because of their peculiar property of obtaining nutrition from dead and decomposing organic matter. With that group of saprophytic micro-organisms which never invades the human body, and often described as *obligate saprophytes*, we here have little to do; but we cannot ignore entirely the great group of saprophytes, since some of its most important members carry on both an extrinsic and an intrinsic existence, so far as the human being is concerned; that is to say, they may be both saprophytes and parasites in the course of their life history, and hence they are called *facultative parasitic*, if preferably saprogenous though capable of becoming parasitic, or *facultative saprophytic*, if by nature parasitic while still capable of flourishing outside of the animal body. Then there is, as far as our present data enable us to judge, a class of micro-organisms which can subsist only in the living animal host, being, therefore, *obligate parasites*.

Parasitism is a product of evolution. This must never be lost sight of in studying any of its manifestations, since many variations will thus be

explained. Parasitism is a late biologic process in point of evolution, having been acquired after the free-living state of organic existence had been perfected. Its various adaptive stages can be seen even now, obligate parasitism representing the highest state of adaptation, with all intermediate variations to the state of obligate saprophytism. This evolution is going on about us day by day, and, recognizing its operation, we are not surprised to find that the list of parasitic organisms is gradually receiving accessions from the saprophytes. Nor is it surprising to find that, as the knowledge of the life history of many microparasites broadens, more importance is attached to the intermediate stages of their evolution.

As in general parasitology, so in the case of the human microparasites, the results of this foreign biologic occupation are various. Two factors must always be considered: the parasite, and the organism invaded by it, or the *host*. The parasite may choose as its abiding-place or *habitat* only the exterior or surface of the host's body, being then *ectoparasitic*; it may dwell solely in the interior of the host's body—in the alimentary tract, in the organs or tissues or circulating fluids—being then *entoparasitic*; or an ectoparasite may find its way into the interior, there to thrive with more or less success. The name parasite, as it is understood in ordinary parlance—a being living at the expense of another—defines the underlying cause of human microparasitology in most cases, the question for the parasite being one of nutrition and life dependent on another living being. The host may be variously affected by this foreign tenant. Often no harm follows, the presence of the parasite being wholly inconsequential. Again, the effect may be one of benefit to the host and of usefulness so great as to be indispensable; but this is not always so, and the parasitic invader exacts from the harboring organism various penalties. These harmful effects are shown by perversions of the normal conditions in the host—by morbid processes local or general, mild or severe—or in other words, by *disease*. So that the group of microparasites which especially concern us at this time is the great class of *disease-producing* or *pathogenic microparasites*. The extreme penalty, that of death, is, unfortunately for the longevity of the human race, only too frequently exacted by these depredatory micro-organisms. But the human organism does not remain passive when infested by harmful parasites, and in consequence the latter often suffer various degrees of restriction in their ravages, leading to a cessation of their activity (manifested in the host by arrest of disease) or to their expulsion or entire destruction (signaled by recovery from disease).

These considerations concerning parasitology apply in general to all parasites, macroscopic and microscopic, animal and vegetable. Our present purpose necessitates attention only to the microparasites; but even these, as has already been remarked, are represented by members both of animal and plant life. At this point, therefore, the first great subdivision of microparasites may be made into *vegetable microparasites* and *animal microparasites*. Of the animal microparasites, we shall consider only the unicellular forms, or protozoa.

Both from their numbers and their relative importance in pathology, the vegetable microparasites are entitled to priority of description. These microscopic disease-producing plants, often classed with the fungi on account of the absence of chlorophyll in most of their representatives, are conveniently divided into three great classes: the *fission-fungi* or *bacteria* (*schizomycetes*),

the *budding fungi* or *yeasts* (*blastomycetes*), and the *filamentous fungi* or *moulds* (*hyphomycetes*). We shall treat them in two parts: (1) The pathogenic bacteria; (2) Pathogenic budding and filamentous fungi.

THE PATHOGENIC BACTERIA.

General Morphologic Considerations.—The minute unicellular plants comprising the great group of bacteria, while apparently of simple structure, are nevertheless but little known so far as the finer morphologic details and their significance are concerned. Much of this lack of knowledge must be ascribed to the excessive minuteness of the bacterial cells, some of which are at the extreme range of microscopic vision as it is perfected to-day. On this account the *classification of bacteria* is still in an imperfect state, and, while much progress in systematic bacteriology has recently been made by the introduction of new methods (like flagella-staining), many of the morphologic features on which an accurate differentiation must be based are still undetermined. None of the schemes of classification thus far advanced is free from objection, but this is not a serious matter so far as the pathologist is concerned. For the present purpose, therefore, the subject of classification will be largely ignored, while retaining that nomenclature most widely accepted. It must be borne in mind, however, that both classification and terminology are far from secure at present.

The primary division of pathogenic microbes according to their shape into *micrococci* (*coccaceæ*, Migula), *bacilli* (*bacteriaceæ*, Migula), and *spirilla* (*spirillaceæ*, Migula) is generally satisfactory, and the subdivision of these families into genera, also on morphologic grounds, is likewise quite acceptable. The final differentiation into species and varieties depends chiefly on physiologic attributes, and here difficulties are encountered. This scheme of classification is useful in practice; its imperfections depend not only on an ignorance of morphologic details, but also on the wide range of variation, both morphologic and physiologic, to which bacteria are subject. This is illustrated by certain well-known pathogenic bacteria, as, for example, the so-called *bacilli* of diphtheria, of tuberculosis, and of glanders; for the tendency now is to remove these organisms from the bacilli family, and to place them among the family of thread fungi (*chlamydobacteriaceæ*, Migula), to which the important class of actinomyces belongs.

As to the general morphology of bacteria, we may say that the pathogenic bacteria are unicellular, chlorophyllless, microscopic plants, varying considerably in shape and size, and very susceptible to changes in environment by which morphologic variations of considerable range are produced. The *cellular substance* seems to be a vegetable protoplasm with certain metaplastic granules reacting like fat, starch, and sulphur. A *cell-wall* bounds this protoplasmic mass and bears a close resemblance to a hardened external layer of mycoprotein, although some species possess a cellular envelope giving the microchemical reactions of cellulose and allied carbohydrate substances. Regarded in the light of analogy with other simple microscopic organisms, it is highly probable that bacteria possess a nucleus, though it remains for future investigation fully to decide this point. Such double staining reactions as bring out the "metachromatic bodies," and those following the application of the Romanowsky stain in certain species, are highly suggestive in this direction. The *capsule* which invests some pathogenic bacteria is often an

artefact due to a swelling and distortion of the cell-wall. In those few species in which it is produced by vital activities, it apparently results from a softening or jelly-like metamorphosis of the outer portion of the cell-wall. Another striking structure, also related to the cell-wall and capsule, is the *flagellum*. These protoplasmic, whip-like appendages of the motile species are presumably part of the cell-wall, and are not in direct continuity with the internal protoplasmic mass.¹ A *sexual differentiation* has not been determined for bacteria, if indeed it exists; although the irregularities manifested by these organisms in shape and size, and the presence of various chromophilic substances within them, may ultimately be shown to have some significance in this direction. This may also be true of the process of flagellation in certain forms, particularly those in which the flagella are set free or assume unusual proportions (like the giant flagella of the malignant edema bacillus).

Multiplication and Reproduction.—According to our present knowledge, bacteria multiply by a process of simple division or *fission* in one or more planes depending on specific characteristics, and by a process of *sporulation*. The latter mode occurs when a resting or resisting stage is called for; the former is the usual method during the active vegetative stage. Of the *endosporous* mode of sporulation, our knowledge is quite precise; but there is considerable obscurity concerning the details of *arthrosporous* reproduction. Probably, as more is learned about sporulation, it will be found that the method of perpetuation by endospores is the common phenomenon among bacteria, judging from analogy with other microscopic fungi and from the prevalence of sporulation or seed-formation in plant forms generally.

Vital Activities.—From the standpoint of pathology, the most significant life phenomenon of pathogenic bacteria is that of *poison-production*, to which brief reference will now be made. That toxic substances are elaborated by bacteria, both within the living host and *in vitro* under experimental conditions, has been satisfactorily demonstrated. To what extent these poisons are generated from the albuminous substratum in which the bacteria grow, and to what extent from the internal metabolic activities of the bacteria themselves, are not determined. Probably both modes of elaboration are called upon in the case of bacteria. In the living body the part played by the living cells and juices is no small one in making up the picture of a given disease. The poisonous products of bacterial activity are the *ptomaines*, a class of crystallizable alkaloidal bodies, generally originating from the bacterial decomposition of dead animal matter; the *toxins*, poisonous substances contained in the bodies of living or dead bacteria or secreted by them; the *toxalbumins*, noncrystallizable and presumably proteid bodies not intimately associated with the protoplasm of the bacterial cell. The so-called *toxoids* are modified toxins in which the original potency has been lost spontaneously, as by age, or by such influences as heat, but which still are capable of conferring artificial immunity. It is to such toxic substances that the pathogenic micro-organisms owe their disease-producing power, contrary to the belief once current that they inflicted damage on account of their presence as foreign bodies in the organs

¹ But it must be remembered that, except in the case of certain large bacteria studied under exceptionally favorable conditions, no one has ever seen flagella in the living bacterium. Certainly nothing is known about their formation and fate from actual observation.

and juices of the host. The invasion of poison-producing bacteria and the sum total of the phenomena attending their presence in the body are known as *infection*. In the course of an infection, however, the animal organism does not remain passive, but through various agencies endeavors to inhibit the activities or to destroy the offending microparasite. Certain cells, both free and fixed, respond to the irritating influences of the parasite, and, by inhibiting or destroying the vitality of the micro-organism and by taking its body into their substance (*phagocytosis*), aid in ridding the body of the invader. Besides this mode of defence, the invaded organism possesses the power of annulling or neutralizing the toxicity of bacterial poisons by virtue of the elaboration of antidotal substances through the agency of its living cells. These protective bodies appear in the animal juices, notably the blood-serum, and several of them are now known. Thus the defensive proteids of natural immunity (inherent in the organism from birth), supposed to be excreted by the leukocytes and to reside normally in the blood-serum, are called *alexins*. Substances which appear during spontaneous or artificial infection or intoxication are known as *antibodies* (*Antikörper*) and *antitoxins*. Still another class of substances resulting from infection or intoxication, also appearing in the blood-serum, is capable of arresting the motility of motile species and of causing coherence or agglutination of the living or dead bacteria; these are the *agglutinins*, and they are closely allied to the *bacteriolysins*, which cause disintegration and solution of the bacteria. The exact nature of these interesting substances, which are all considered as proteids, has not been fully determined; but the most popular assumption is that they are unorganized ferments or enzymes, and on this basis Ehrlich and Morgenroth have recently elaborated an hypothesis to explain their function in immunity.

THE PRINCIPAL PATHOGENIC BACTERIA.

The Bacillus of Anthrax.—It was the discovery of the anthrax bacillus as the essential cause of anthrax that constituted the first satisfactory demonstration in pathologic bacteriology.

The specific micro-organism of this affection is a comparatively coarse bacillus dividing by fission in the vegetative state, leaving partition-lines that are usually plainly visible, and tending to form long chains when dividing in unhampered surroundings. A resisting stage with formation of median endospores is also a part of the life history of this bacillus, although it never forms spores in the body of the living host. The range of morphologic variation is not wide, the chief being in the length of the rod and in its thickness. In the animal organs and juices it tends to become a shorter rod than in artificial media, and an envelope, apparently a true capsule, appears about it in stained preparations, especially of anthrax blood. The physiologic characteristics of the anthrax bacillus are also unusually constant, both in natural and artificial environment. Except for a slight deviation in proteolysis and rate of growth, artificial anthrax cultures show little change even after prolonged stay in the laboratory, and the pathogenic activity of the bacillus is retained with unusual persistence under artificial conditions. On this account and because of the readiness and certainty of its effects in susceptible animals, it is the favorite bacterium for laboratory experimental demonstrations.

In all probability this bacillus had its natural habitat in surface soil or upon surface vegetation like grass, and passed here the saprophytic stage of its evolution. From this normal

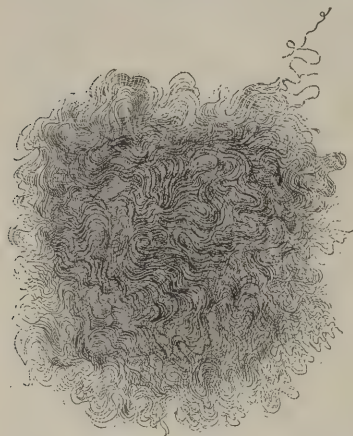


FIG. 75.—Colony of bacillus of anthrax, slightly magnified (Flügge).

abode it found its way as a parasite first into grazing animals, hence the wide natural prevalence of anthrax among wild and domesticated ruminants. Infection in man does not seem to be possible except through an intermediate animal host, and most commonly the disease follows the handling of infected living or dead sheep and cattle, their hides, and the bristles and hair of animals dead of the disease. Possibly suctorial insects may also carry the infection from these animals to man, but direct contact with the affected animal or a product derived from it can usually be demonstrated as the mode of invasion. Woollsorters' disease is anthrax commencing in the respiratory organs, and is due to inhalation of infective dust or wool-fibers. Swallowing the material may produce intestinal anthrax, and there is reason to believe that eating underdone meat of infected cattle or sheep may incite the same infection.

Morbid Action.—Anthrax in man is a disease not clinically uniform.

This irregularity depends principally on the avenue of invasion, of which there are three chief ones—the skin, the respiratory mucous membrane, and the intestines.

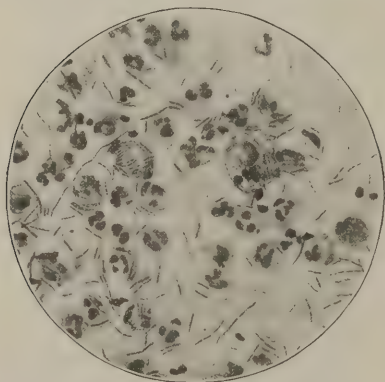


FIG. 76.—Anthrax bacilli in exudate, showing phagocytosis. $\times 300$ (Karg and Schmorl).

The characteristic anatomic lesion of cutaneous anthrax is the malignant pustule—a circumscribed, discolored swelling of the surface, varying in size within moderate limits and resembling somewhat an ordinary furuncle. Its color is usually a deep reddish, and the surface may be smooth or broken and covered with dried secretion, or it may be blackened and necrotic in older lesions, resembling a miniature volcanic crater, from which issues a

purulent or seropurulent and often bloodstained discharge. It is often surrounded by vesicles like a string of pearls. In its early stages the pustule is indurated, then it becomes succulent, and finally filled with fluid or semifluid purulent material. This cutaneous focus owes its origin to the positive chemotactic influence of the bacillus and its products, resulting in the accumulation of a serosanguinolent and cellular exudate in the papillæ and the corium, the latter layer becoming packed with multinuclear leukocytes. In the superficial

portions and the papillary body the anthrax bacilli are encountered, usually in large numbers, dispersed both in the blood-vessels and in the spaces of the tissues or between the cells of the exudate. In chronic malignant pustule the bacilli may be entirely wanting. The densely accumulated leukocytes seem to make a barrier against the deeper progress of the micro-organisms. In different individuals there seems to be a marked variation in the number of bacilli in the pustules, in their diffusion, and especially in the phenomenon of phagocytosis. The latter process is very active in some cases, most of the polynuclear leukocytes and large mononuclear hyaline cells in a smear-preparation of the discharge containing bacilli in various stages of disintegration. Even where phagocytosis is not so pronounced, there seems to be a harmful influence at work upon many of the bacilli, which fail to stain in the usual manner. Both in malignant pustule and in general anthrax infection the principal changes are a serous, serofibrinous, or seropurulent inflammation with more or less hemorrhage and necrosis. There is frequently a cloudy swelling of the viscera, and the spleen is so swollen as to give the synonym "splenic fever" to anthrax, although this is not invariably present in man. But fatal general anthrax may occur in man, with lesions so insignificant as not to attract attention, producing a veritable anthrax septicemia. Hemorrhages are frequently observed in the alimentary mucosa in intestinal anthrax, and have also been noted in the mesenteric and bronchial lymph-glands, the pancreas, and the brain. Necrosis and ulceration may appear in the hemorrhagic areas. A metastatic embolic infection of the gastric and intestinal mucosa, with resulting hemorrhagic necrosis and submucous edema, has been occasionally seen in cutaneous malignant pustule. Other anatomic lesions inconstantly noted in anthrax are tonsillitis, bronchitis, pneumonia, pleuritis, adenitis, endocarditis, and peritonitis.

So filled are the capillaries of infected viscera, like the liver, with anthrax bacilli, that the theory of mechanic plugging was for some time held to explain the pathogenic action of these bacteria. The filling of the capillaries in the important viscera and a decomposition of the blood were considered as the principal factors. This theory is no longer held, its inadequacy being shown, for instance, by the cases of fatal anthrax with few or no bacilli in the blood-vessels of important organs. Gradually it was learned that poisonous products were elaborated by the growth of anthrax bacilli under artificial environment, and some of these products were fatal when used on susceptible animals, although not followed by typical symptoms. Some confusion as to the exact identity of this anthrax toxin still exists, but most authorities maintain that it is only on the basis of a toxic action that the phenomena of spontaneous or experimental anthrax can be explained. Whether the blood-vascular or lymph-vascular channels are chosen for the spread of the organisms from the primary focus is not positively determined, though the latter route seems the more probable one; and the enormous increase of bacilli so often seen in the blood-vessels is to be regarded as a late or agonal phenomenon in the disease, the progress of which to this point results from the toxemia. Evidence in favor of this presumption is afforded by the equally slow progress of intravenous and subcutaneous experimental anthrax and by the more rapid course of the disease when beginning in regions well supplied with lymphatics, like the face, neck, and mucous membranes.

Historically it is of interest to note that anthrax is one of the infectious diseases in which bacterial therapy was first attempted. Pasteur and his followers tried to produce an active immunity in sheep by vaccination with an anthrax virus attenuated by heating virulent cultures. As now perfected, this protective vaccination in sheep and cattle has a practical commercial value, although the results are not always certain and the period of immunity is often quite short. Anthrax is also one of the infections in which experiments in serum immunity were first tried, but thus far the results in this direction have not been encouraging from the therapeutic standpoint.

The Bacillus of Typhoid Fever.—No one who works with the two groups of bacilli, the colon and the typhoid, and especially with the intermediate forms, can fail to be impressed with the narrow margin of physiologic differentiation separating them. Many are now inclined to consider the typhoid bacillus as a modified colon bacillus, as a fecal bacillus unaltered morphologically, but with a few acquired physiologic characters probably due to its more or less prolonged sojourn under saprophytic conditions. This view, proclaimed by Rodet and Roux about ten years ago, has

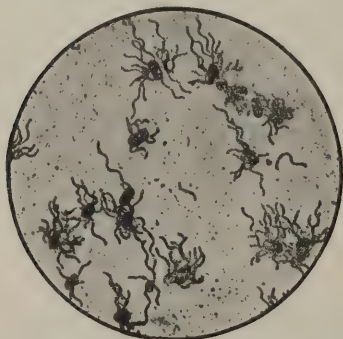


FIG. 77.—Bacillus of typhoid fever, from an agar-agar culture six hours old, showing the flagella stained by Löffler's method. $\times 1000$ (Fränkel and Pfeiffer).

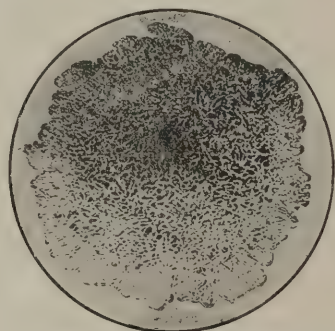


FIG. 78.—Bacillus of typhoid fever: superficial colony two days old, as seen upon the surface of a gelatin plate. $\times 20$ (Heim).

been steadily gaining ground, although it is by no means firmly established. It seems, however, to explain most readily the otherwise anomalous behavior of typhoid fever under natural conditions, both with reference to its clinical and pathologic features.

At present we are inclined to regard the morphology of the typhoid group as more constant than that of the colon bacillus, although this may only be a matter of limited observation. Both are nonsporogenous, the clear spaces in the bacterial cell, once supposed to be spores, resulting from plasmolysis. The physiologic differential features of the extreme types, as we study them under the artificial conditions of the laboratory, seem sufficiently marked to be distinctive. It is only when the intermediate or linking types are studied that skepticism is aroused as to the fixed nature of such characteristics as the fermentation reaction, milk coagulation, indol production, and the like; and even the agglutination phenomenon can scarcely be said to have an absolutely fixed value.¹

¹ One of the most significant arguments for the close relationship of these bacterial groups seems to be afforded by the now generally adopted practice of "rejuvenating" bacilli

Although the typical specific bacilli have only occasionally been demonstrated in drinking-water, the latter is nevertheless held to be the usual medium of contagion, becoming contaminated from the feces or urine of previous cases of typhoid. It appears that the organism may occasionally be carried by other foodstuff, like milk or oysters; and by certain plants, as radishes or celery, contaminated with infectious material like sewage, or washed with contaminated water. The longevity of the typhoid bacillus even in distilled water is considerable, and it probably leads a prolonged existence under more favorable nutritive saprophytic conditions. Another mode of contagion, the importance of which is being more and more recognized, is by means of certain insects, particularly flies, which feed upon human dejecta and then light upon various articles of food; upon this hypothesis certain extensive outbreaks of typhoid fever in military camps have been explained. Here the fly does not act as an intermediate host, but only as a mechanic carrier of the parasites. The possibility of air-borne typhoid must be admitted, although it has not been proved. In most cases the feces and

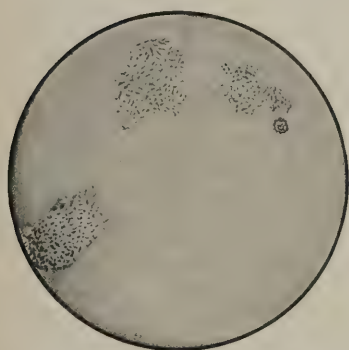


FIG. 79.—Typhoid bacilli, showing the Widal agglutination reaction (Slater and Spitta).

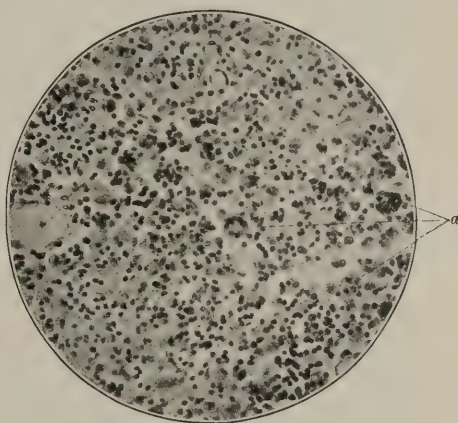


FIG. 80.—Medullary swelling in a typhoid lymph-gland in a state of large-celled hyperplasia, showing at (a) large multinuclear cells (macrophages), $\times 235$ (Karg and Schmorl).

urine of typhoid patients appear to furnish the infecting germs, their presence in large numbers in both having been positively determined.

Morbid Effects.—That bacilli of the typhoid group are the essential etiologic factors in human typhoid fever seems satisfactorily demonstrated, even though experimental proof, such as may be obtained in some other microbial affections, has not been secured. Typical typhoid fever presents a clinical and anatomic picture of remarkable uniformity, and in all well-developed cases the typhoid organism may be found in the spleen and mesenteric lymph-glands. The fundamental gross lesions are swelling and, later, of the colon group secured from saprophytic surroundings, as from water, by growing them for several generations under the artificial laboratory environment before making physiologic differential tests. In the early generations on plate cultures, much divergence is manifested by the progeny of the individual organisms; and to overcome this and reduce them to the "normal" typical condition, they must be rejuvenated. It may well be doubted whether the characteristics remaining from the saprophytic sojourn, or those acquired under laboratory environment, are really the normal. Many of the acquired characteristics make a suspiciously typhoid-like behavior in a so-called colon bacillus.

ulceration of the solitary and agminated lymphoid follicles of the intestinal mucosa (ileum, or ileum and colon), the tumefaction of the mesenteric nodes and of the spleen. More intense infection is shown by cloudy swelling of the viscera and by further changes, like cholecystitis, cystitis, pneumonia, laryngitis, osteitis, meningitis, etc. Thrombosis, especially of the larger veins, is rather common as a complication. The point of excitation in typical cases seems to be the lymphoid follicles of the ileocecal region, and in mild cases the intestinal lesions are confined to this locality. A diffuse swelling of the solitary glands and Peyer's patches appears, extending up the small bowel and sometimes into the colon, and the mesenteric glands also swell, those in the line of absorption from the ileocecal region first. From the more recent and precise histologic studies, especially those by Mallory, it appears that the tumefaction of the intestinal, mesenteric, and splenic lymph-apparatus is due to the excessive proliferation of phagocytic endothelioid cells arising from the lymph-spaces, lymph-vessels, and endothelial layers of the blood-vessels. These cells are diffusely scattered throughout the swollen follicles and glands in immense numbers, or accumulated in large groups; and they manifest pronounced phagocytic activity, as well as multiplication, or retrogressive changes. In the finer blood-vessels they may occlude the lumen, such occlusion being often accompanied by a deposition of fibrin. In some cases the appearance of similar intravascular plugs in remote organs is probably of an embolic nature, although an endothelial proliferation may apparently be excited in the tissue-spaces and blood-vessels of parts remote from the abdomen.

Peculiar collections of cells in the liver, formerly known as lymphoid nodules, are quite constant in typhoidal affections; these are now known to be focal areas of coagulation-necrosis. They may also appear in the kidneys and in the spleen, and in some cases at least they are related to a minute blood-vessel occluded by an endothelioid cell-mass or a fibrinous, or cellular and fibrinous, thrombus. In other foci no connection with occluded vessels can be seen, the accumulations seemingly being induced by the local outpouring of some toxic fluid from the vessels.

The typhoid bacillus at times exhibits pyogenic properties; and abscesses of the mesenteric glands, spleen, liver, and bones, as well as suppurative cholecystitis, pleuritis, and meningitis, may be caused by it. The pulmonary affection of typhoid fever usually takes the form of bronchopneumonia, in which aspiration-infection plays a role, the lesion containing either foreign bacteria alone or such bacteria and the typhoid bacillus. Lobar or croupous pneumonia also occurs—the result, as a rule, of infection with the pneumococcus. Typhoidal meningitis may take the form of a hemorrhagic pachymeningitis, of serous or suppurative leptomeningitis. In the latter case the exudate consists both of ordinary pus-cells and endothelioid elements, and may be accompanied with an obliterative endarteritis due to subintimal accumulations of small round cells.

Atypical typhoid fever with no trace of intestinal ulceration and little or no lymphoid swelling of the intestinal mucosa, taking the form of a septicæmia, has been repeatedly noted. But it is more common for the bacilli to confine themselves to the intestinal lesions, mesenteric glands, spleen, bone-marrow, and gall-bladder, instead of invading the general blood-stream; so that the extensive histologic alterations above noted must, in part at least,

be ascribed to some product of bacterial, or bacterial and cellular, activity. As to the nature of this toxic substance, but little is known; in any case, the poison is not powerful, and the results of experimental efforts to induce typhoid fever by the use of living or dead bacilli, or substances extracted from them, have been rather indefinite.

Immunity and Bacterial Therapy.—Positive knowledge concerning the source and nature of the typhoidal poison is still unattained, the general view being that the substance is contained in the bodies of the bacilli, although other evidence suggests that, in the animal body at least, a diffusible toxic agent is liberated. Experiments in artificial immunity are not satisfactory, for the reason that laboratory animals are for the most part susceptible only to intraperitoneal injections, which produce merely a peritonitis. Subcutaneous abscesses have been obtained experimentally, and purulent meningitis by subdural inoculation; and death sometimes follows large subcutaneous injections. But animals may be immunized by gradually increasing doses of living or dead typhoid bacilli, the peritoneal cavity becoming more and more resistant to infection, and the serum of such animals develops a specific bactericidal (bacteriolytic or disintegrating) property against the typhoid bacillus, becoming a weak antitoxin with both protective and curative action. Practically typhoid antitoxic serum has been a failure; but protective vaccination with attenuated typhoid cultures, which has been extensively carried on in the British army in Africa, is more promising. The composition of the bactericidal and antitoxic agent in the serum of animals made immune by artificial means or by reason of an attack of typhoid fever is undetermined, and the same must be said of the so-called agglutinins, which give to the serum its capacity of causing agglutination of typhoid bacilli. This does not, of course, detract from the wide and successful application of the agglutinating or clumping reaction in clinical diagnosis.

The Colon Bacillus.—Soon after birth the intestines of man—and most, if not all, other mammals—are occupied by this parasite, which has been found in the intestinal contents of most vertebrates. Both its widespread occurrence and its existence in healthy animals suggest that the colon bacillus occupies an important part in the animal economy. It seems, however, that the early development of newborn guinea-pigs is not impeded by keeping these organisms out of the bowels; but how far this is applicable in more prolonged existence, or in man, experimental facts do not show. In a state of health in adults, there can be no question of the usefulness of the intestinal flora in which *Bacillus coli communis* predominates, as it doubtless aids in digestive operations and contributes to the formation of gas so necessary to the maintenance of abdominal and thoracic equilibrium. Being so constant, if not indispensable, an inhabitant of the intestines of vertebrates, and being evacuated with their feces, it is not surprising that the members of this group are found widely distributed in nature; and when one considers all the various vicissitudes to which animal feces are subject, entailing great changes in the environment of the contained bacteria, the

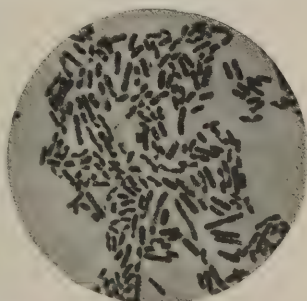


FIG. 81.—*Bacillus coli* (vacuoles). $\times 1000$ (Migula).

numerous subvarieties of the colon group seem, in part at least, explicable. That members of the colon group of bacteria are subject to wide physiologic variation is well known—there being, indeed, a chain of varieties reaching from the colon to the typhoid group, as already indicated. The extreme so-called “typical” colon bacillus causes fermentation and proteolysis, produces indol, and coagulates milk; but these functions show gradual modifications among the intermediate varieties. Morphologic variation is not striking among the colon bacilli cultivated in the laboratory, but extreme deviation from the ordinary rod has been noted of late in careful examination of organs, like the liver, harboring old latent bacilli of the colon group or recently infected. Here the micro-organism may appear as long threads, or shorter, broken streptococcoid threads, or micrococcoid (diplococcoid) forms, some of extreme minuteness. A failure to recognize atypical forms has undoubtedly led to occasional faulty diagnosis of the bacterial species, since the irregularities may persist for several generations on artificial culture media.

Under conditions almost wholly unknown to us at present, this harmless or even useful bacterial messmate may become a harmful, deadly enemy, at times apparently beginning its pathogenic activity in the intestinal canal, which constitutes its home. Infantile diarrhea, diarrheal affections in adults, and certain dysenteries may be all due to bacilli of the colon group, at times quite typical, at others more or less atypical. In some of these cases there is little anatomic change, the process being incited by irritating foodstuffs or by perverted and toxic digestive products, which induce a lowered resistance, thus opening a way for the ravages of the bacteria. Under other circumstances, as in the case of appendicitis, strangulated hernia, intussusception, etc., mechanic lesions of various kinds may precede the destructive activity of the colon bacilli. Invasion of the gall-bladder and bile-ducts often follows injury from biliary calculi, although it is not positively determined whether the bacilli gain access from the bowel or by the blood. Exogenous infection by these organisms is also possible, as seen occasionally in wound infections. Foods contaminated by colon bacilli from outside sources have been at times found responsible for outbreaks of extensive food-poisoning, taking the type both of an intoxication (botulismus) and of an infection.

Morbid Effects.—An inflammatory reaction, sometimes suppurative, usually attends the advent of pathogenic colon bacilli in the human body. Almost any organ or any serous surface may be incited to inflammation, generally of an acute nature, and which is often followed by the production of serofibrinous or fibrinopurulent exudates. At times the colon bacillus alone plays the role of a pyogenic organism, although in the most severe manifestations of its activity, as in appendicitis and peritonitis, it is often mixed with the pyogenic cocci. It is responsible for many inflammations of the genito-urinary tract, particularly pyelitis, rarely also urethritis. Focal coagulation necrosis may be produced in spontaneous or artificial infections with this organism. Occasionally, in chronic and prolonged irritation with bacilli of the colon group—occurring, for instance, in neglected or unrecognized appendicitis—a large amount of new fibrous connective tissue with hyaline degeneration will form, and give rise to the production of more or less localized tumor-like masses occasionally mistaken for true tumors. Abscesses and fistulas may form in such masses. Whether a somewhat similar process, resulting in the production of fibrous tissue in the parenchyma of organs, as in the

liver and kidney (cirrhosis), may be induced by the colon bacillus or its allies (so-called paracolon bacilli), is still unsettled, although certain investigations point strongly to this conclusion. An acute and rapidly fatal process taking the form of a septicemia also at times occurs in the course of an acute or subacute colon-bacillus infection.

Immunity and Bacterial Therapy.—The poisonous substance produced by the colon bacillus, to which its various pathogenic effects are due, is, like that of the typhoid bacillus, not definitely determined; but, as in the case of the latter, it is supposed to reside, for the most part at least, in intimate combination with the protoplasm of the bacterial cell. Experimental infections with the various colon bacilli bear a close resemblance to those produced by the bacillus of typhoid fever, essentially the same phenomena as to immunity, agglutination, and the production of a protective or curative serum being witnessed. No therapeutic results of practical value have as yet been obtained, except perhaps in acute tropical dysentery.

Pathogenic Bacilli Resembling the Colon-Typhoid Types.—

Besides the more typical members of the typhoid and colon groups of bacilli, a large number of nonpathogenic and pathogenic bacilli have been described, which show but a shade of deviation, chiefly in physiologic differential tests, from one or another of the types. Some of these organisms, which many observers believe are but varieties of the colon or typhoid species, are associated with important pathologic processes, and several of them are doubtless destined to assume great importance in pathology. Thus there is a group sometimes separately considered as *Bacillus enteritidis*, to which several subspecies belong, the features of which are strongly suggestive of relationship with the colon bacillus, and which are concerned in various diarrheal disorders and intoxications caused by their presence in meat. Also allied to this group are the *hog-cholera bacillus*, now generally accepted as the exciting cause of this disease in swine, and, more important still, the so-called *Bacillus icteroides*, claimed to be the micro-organism of yellow fever. Both these organisms present biologic evidence of affinity with the human colon bacillus; moreover, they resemble each other so closely that certain investigators have considered them identical. Both are pathogenic under experimental conditions, producing necrosis and showing other evidence of similarity as to their toxic products, immunizing substances, and agglutinins. In the dog, the *Bacillus icteroides* causes symptoms and lesions suggestive of those in yellow fever, and strong claims are made for the specificity of this micro-organism. No matter what view may be taken about the relationship of the hog-cholera and yellow-fever bacilli, it must be remembered that both these micro-organisms are closely allied to the larger colon-typhoid group, and that climatic and environmental conditions and peculiarities in the host may account for the slight variations which the bacteria show and for the wider variation exhibited by the diseases which they are supposed to induce. Such consideration also applies to other typhoid-colon forms, as *B. dysenteriae* and *B. paradoxus*, obtained from cases of acute tropical dysentery, and by some believed to stand in a causal relationship, and to the *paracolon bacillus*, *pseudotyphoid bacillus*, *bacillus of mouse typhoid*, and a number of other organisms, variously designated by different investigators.

Bacillus Mucosus Capsulatus (*the Pneumobacillus of Friedländer and its Related Forms*).—As the type of a large group of bacilli, which agree in general cultural behavior and in the possession of a capsule (espe-

cially when obtained from animal secretions), we may consider the pneumobacillus of Friedländer. To this group, which comprises a large number of asporogenic, nonmotile bacilli described under different names by various observers, the designation *Bacillus mucosus capsulatus* has been given by several recent writers, who have systematically studied the various members.¹ The various individual representatives of the group, which are regarded as varieties or subvarieties, have been further divided into two chief classes, those more closely related to the pneumobacillus and those resembling the ozena bacillus, which stand as the extremes of the series. Polymorphism is characteristic of these bacilli, so that no system of morphologic classification is reliable. True capsular envelopes are formed by all the legitimate members of the group, sometimes when grown on an artificial medium, like blood-serum, sometimes only in the blood or juices of infected animals, sometimes under both conditions. So constant is this morphologic feature that from it the name *B. mucosus capsulatus* has been derived. In a general way, the physiologic characters are those ascribed to the typical Friedländer bacillus;

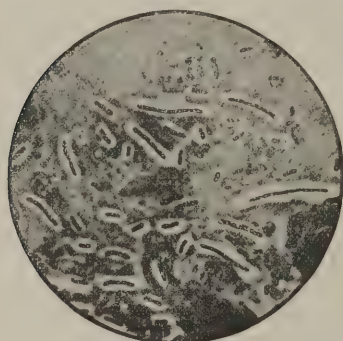


FIG. 82.—*Bacillus mucosus capsulatus* from the sputum of a pneumonia patient. $\times 1000$ (Fränkel and Pfeiffer).

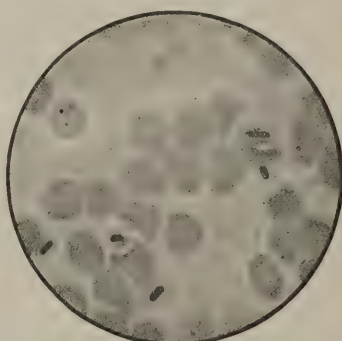


FIG. 83.—*Bacillus mucosus capsulatus* in blood. $\times 1000$ (Fränkel and Pfeiffer).

that is, a slimy, mucoid, profuse growth on agar and blood-serum; a somewhat similar yellowish growth on potato; a nonliquefying growth along the line of the gelatin stab, with a rounded, glistening, subspherical ("nail-shaped") elevation at the surface; variable fermentative function; no indol production or proteolysis; and decolorization by Gram's method of staining. The cultural variations for the whole group are comparatively slight; but the capacity of fermenting the sugars is subject to much variation, some members of the group never producing gas, and others causing abundant gas formation in media with various sugars. Staining after Gram's method occurs at times. Many of the cultures have an aromatic odor, some are odorless, others fetid. The pathogenicity of this group, as tested by subcutaneous, intraperitoneal, or intrapleural injections in mice (particularly white mice), guinea-pigs, and rabbits, is also an inconstant feature. Almost all of the members prove pathogenic for mice in subcutaneous inoculations, although

¹ In this group are included, among others, the *Rhinoscleroma bacillus*, *Proteus hominis capsulatus*, *Bacillus capsulatus* of Pfeiffer, of Mandry, of Kockel, of Loeb, of Cohn, of Mallory and Wright, of Chiari, etc., *Bacillus mucosus capsulatus* of Fasching, of Paulsen, of Abel, etc., and still others, twenty-two in all, enumerated by Fricke in his analysis of the group. *Bacillus lactis aerogenes* is also closely allied with the group of capsulated bacilli.

some, like the typical pneumobacillus, only prove fatal when inoculated into the peritoneal cavity or the lungs. A few do not kill mice. Guinea-pigs prove refractory to several capsulated bacilli, and rabbits to others. Sometimes one and sometimes another of these species of rodents will succumb to the infection, while in a few instances all three species react.

Evidently the pneumobacillus and its allies belong to a group of facultative saprophytes, since they have been found in dust, mud, air, and canal-water. At times they appear in the nose, mouth, trachea, and intestines of healthy human beings.

Morbid Conditions with which *Bacillus Mucosus Capsulatus* is Associated.—These organisms have been found in a variety of pathologic conditions, at times alone, and again in company with other pathogenic bacteria. In some instances they appear to be the sole exciting factor of the morbid process.

The first disease in which the capsulated bacilli were found, and which led to the designation pneumobacillus,¹ was *pneumonia*, from which the organisms were isolated and studied by Friedländer in 1883. We now know that in 5 to 10 per cent. of cases of croupous pneumonia in man, and in a somewhat higher percentage of cases of bronchopneumonia, these capsulated bacilli are found, usually mixed with other micro-organisms. That it can cause typical acute lobar pneumonia is doubtful; but there is no question as to its etiologic role in other forms of pneumonia, especially bronchopneumonia.

As complications of the pulmonary affection, such lesions as *pleuritis*, *pericarditis*, *endocarditis*, *bronchitis*, *otitis*, and *meningitis* have been observed, with capsulated bacilli in pure or mixed cultures. Infection of the genito-urinary tract with the production of pyelonephritis has been ascribed to members of this group; and they have further been found in puerperal metritis, pulmonary and hepatic abscess, gastro-enteritis, and in various catarrhal conditions of the upper air-passages, including the accessory nasal sinuses. In all these situations an acute or chronic inflammatory reaction, usually with suppuration, is induced. Still more important is the association of capsulated bacilli with *hemorrhagic septicemia*, and several well-authenticated cases of this disease in the newborn and in adults are now recorded, in which bacilli with practically identical morphologic and physiologic features were obtained in pure culture. Aside from the cutaneous, submucous, and subserous hemorrhages found in this malady, which seems to be a distinctive affection with some clinical affinity with typhus fever, there are marked changes in the blood-vessels, with fatty degeneration of the endothelial lining, leading to rupture and hemorrhage. A profound destructive effect is also produced on the red blood-cells, the pigment of which accumulates in the liver, spleen, and kidneys. Emboli of liver-cells have been noted. In atrophic rhinitis, especially the form accompanied by fetid purulent secretions (*ozena*), one of the bacilli of the group is so often found as strongly to suggest an etiologic significance. Likewise in rhinoscleroma,

¹ In his original communications Friedländer called this organism a micrococcus (*pneumococcus*), and from some of his descriptions it looks as though he must at times have had *Micrococcus lanceolatus* under observation, especially in smears of pneumonic sputum, exudate from the lungs, and in the blood of animals. But the cultures on nutrient jelly all seem to have been those of capsulated bacilli with the nail-shaped character. It is now conceded that Friedländer erred in attaching too wide an etiologic significance to his "*pneumococcus*."

a chronic granulomatous affection beginning in the nose and often extending to the adjacent mucous or cutaneous surfaces, capsulated bacilli are found, especially as inclusions in large vacuolated cells of the granulomatous tissue and in the secretions, and these bacilli are now placed in this group.

Practically nothing is known concerning natural and artificial immunity against pneumobacilli, and efforts to establish specific agglutination tests for differentiating the various forms have thus far given inconstant results.

Proteus Vulgaris and Related Bacilli.—There is a group of bacteria apparently composed of a number of varieties, as the prototype of which *Proteus vulgaris*, or *Bacillus proteus* of Hauser, may be selected.¹ As originally described by Hauser in his work on putrefactive bacteria, the proteus bacilli are pre-eminently saprophytic, being the common organisms of putrefaction in dead animal and vegetable substances. The widespread occurrence of these organisms is evident from their relation to the putrefactive processes, and their presence in such media as air, soil, dust, water, and in various putrefying foodstuffs, is readily understood. Bacteriologists were for some time inclined to consider these bacilli as obligate saprophytes, and their occasional appearance in the human organism as a purely accidental occurrence. That this is in part true is evident from the fact that the bacteria of this group are found in such places as the mouth, stomach, and intestinal contents of healthy human beings. But there is overwhelming evidence that the harmless saprophytic proteus, under certain conditions, may assume a definite pathogenic role, either aiding in their harmful action other disease-producing micro-organisms, like the bacillus of diphtheria, the pyogenic cocci, the bacilli of tetanus and malignant edema, or pursuing an independent course as the excitant of morbid processes.

Variations in morphology are frequent among these bacilli; micrococcus-like forms, ordinary bacilli, and long filaments often appear in the cultures of a single race. Active motility and a profusion of flagella arranged radially about the bacterial cell are characteristic of most varieties of the group. The members most closely allied to the *Proteus vulgaris* type liquefy gelatin, and in gelatin plates a "swarming" or ameboid-like formation of offshoots occurs during the early liquefaction of a colony. Putrefactive odors are evolved during the peptonization of gelatin and blood-serum. Milk is coagulated and the casein digested. Indol and phenol are formed, and the sugars, with the exception of lactose, are fermented. Spores are not formed, and the growth is facultative anaërobic. These characters are subject to some variation, since certain members of the group have no peptonizing power, while of those having this function some liquefy rapidly and others tardily. The reaction to Gram's stain is inconstant. Moreover, it is claimed by some observers that particular methods of artificial cultivation are successful in changing several of the physiologic characteristics of a given race. In their pathogenic effects on laboratory animals, various proteus bacilli differ markedly. Some are seemingly harmless even when employed in large doses; others induce a chronic intoxication after injection. Following a subcutaneous injection, gradually spreading induration with cheesy metamorphosis may be induced, the animal dying finally in a condi-

¹ Other bacilli closely allied with *Proteus vulgaris* ("*Bacterium termo*" of the older microscopists) are the *B. albus cadaveris*, *Urobacillus liquefaciens*, *B. foetidus ozæne*, *B. proteus septicus*, *B. proteus lethalis*, *B. murisepticus pleomorphus*, *B. proteus fluorescens*, *B. dysenteriae liquefaciens*. *Proteus mirabilis* and *P. Zenkeri* are very similar to the typical *P. vulgaris*, if not identical with it.

tion of cachexia. But many cultures are actively pathogenic, producing prompt fatal results either by subcutaneous, intraperitoneal, or intravenous injections.

Pathogenic Effects in Human Beings.—The proteus group belongs to that rather small class of bacteria which excite disease indirectly through the contamination of material ingested as food. This effect is, of course, what would be anticipated from the constant association of these organisms with putrefaction and decomposition. An epidemic of meat-poisoning accompanied by hemorrhagic enteritis has been traced to proteus bacilli; and we have the record of an extensive outbreak of food-poisoning, characterized with vomiting, fever, and diarrhea, in which oatmeal containing proteus and colon bacilli seemed to be the cause.

Numerous instances of more direct pathogenic action of the proteus bacilli have accumulated in recent years; in many cases the proteus was associated with other pathogenic bacteria, as has already been mentioned. Thus in infected wounds, particularly those of a gangrenous or putrefactive tendency, proteus has been found with other micro-organisms; this is also the case in such conditions as ulcerative endometritis, in osteomyelitic pus, in ozena, and it is questionable whether the proteus here plays only a saprophytic role or is in part responsible for the pathologic process. In such affections as puerperal parametritis, meningitis, and brain-abscess (following middle-ear disease), gangrenous and purulent peritonitis, pulmonary gangrene and gangrenous pleuritis, proteus, while mixed with other micro-organisms, seems to take more than a passive part. Finally there are a number of conditions in which proteus alone was found; from the experimental evidence, it is highly probable that it may have been the sole pathogenic agent. In the last category comes a case of general peritonitis, one of appendicitis complicating an inguinal hernia, pleurisy, several instances of cystitis and pyelonephritis, ovarian abscess, mammary abscess, and liver-abscess. Proteus, in company with the colon bacillus, has been found in cholera infantum and in epidemic dysentery.

More serious still are the general proteus infections, in a number of which now recorded these bacilli appear to be the specific factors. Weil's disease (acute febrile icterus), epidemics of which sometimes occur, is ascribed to the action of a fluorescent member of the proteus group, which has been found unmixed in the urine, blood, and organs of fatal cases, the early observations of Jäger having been confirmed by several subsequent investigators. Probably some cases of infectious icterus and icterus gravis of the newborn, in which proteus was found, belong in the same class as Weil's disease. Proteus has also been described as the causative factor in several examples of hemorrhagic septicemia, where the original infection probably resulted from eating spoiled meat. In at least one instance the disease was epidemic, taking the form of hemorrhagic enteritis with fatal septicemia, thrombosis, hemorrhagic foci in the serous membranes and viscera; here an extremely virulent proteus race was obtained. The recent studies on the kedani disease of Japan are extremely interesting as examples of proteus infection through the wounds inflicted by an insect, a specific mite (kedani) closely allied to the harvest-mite (*Leptus autumnalis*). This epidemic disease, causing a mortality of about 40 per cent., appears in certain river-bottoms (after flood-water has subsided and decaying vegetation remains behind), infecting the individuals who harvest the hay and other fodder and are

bitten by the mites. After a brief incubation period characterized by local reaction at the site of puncture, the lymph-glands adjacent to the region bitten by the insects become swollen and painful, and further swelling affects the remote lymph-nodes. There is fever, running a typhoid-like course, and an urticarial exanthem. Nervous symptoms, bronchitis, and splenic tumor develop, usually with constipation; albuminuria follows, and death results in from ten to thirteen days. From the blood and organs of fatal cases a virulent bacillus with morphologic and cultural affinities with proteus has been repeatedly isolated. Toxic substances have been obtained in dead or filtered proteus cultures, and experimental immunity has been conferred on guinea-pigs either by the use of living bacilli in small doses, by dead bacilli, or by filtered cultures. The blood-serum of these animals possesses protective properties; it also agglutinates the proteus bacilli.

Bacillus Pyocyaneus.—There are bacilli constituting a class or group, of which the pathogenic *B. pyocyaneus* of Gessard makes one extreme, and the nonpathogenic, saprophytic *B. fluorescens liquefaciens* the other. Just how closely these races are united

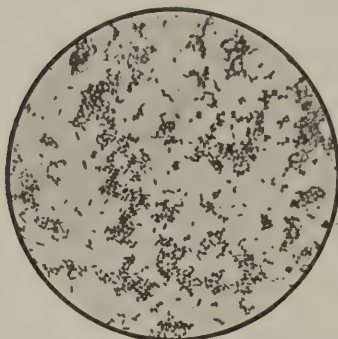


FIG. 84.—*Bacillus pyocyaneus*, from an agar-agar culture. $\times 1000$ (Itzerott and Niemann).

is hard to decide, although the finding of various intermediate varieties tempts one to consider the pyocyaneus bacillus as a liquefying fluorescent bacillus, somewhat modified by adaptation to a parasitic existence. It certainly is suggestive to find that a culture of the fluorescent bacillus obtained from saprophytic environment may assume pathogenic properties after laboratory cultivation, and also to know that pyocyaneus bacilli have been encountered as transient parasites in the saliva, sputum, sweat, and gastric contents from human beings, here apparently leading a semisaprophytic existence, with no pathogenic proclivities.

In morphology, the members of the pyocyaneus group thus far identified as pathogenic are not uniform; for while they generally assume a slender bacillary form with single terminal flagellum, the plump micrococccoid and longer thread-like and irregular forms are to be found in some instances. Active motility seems to be an inherent characteristic, and among the physiologic functions that of coagulating milk is least variable. Gelatin is always liquefied by the members now included in the pyocyaneus group, although the rate of liquefaction differs. Indol is not produced by all the races, and none of them is known to ferment the sugars. Some reduce the nitrates to nitrites. The chief physiologic characteristic of this group of bacilli, and the one by which they are best known, is the property of producing fluorescence and pigments. The pigments elaborated during the active growth of the bacilli in culture media are readily differentiated by physical and chemical tests; sometimes only the fluorescent pigments are formed, sometimes only pyocyanin, more often both. It has recently been proposed to classify the members of this group according to the variations in pigment production. The property of forming fluorescence and pigments is often lost in cultures kept under artificial conditions, and, of the two, that of

forming pyocyanin first disappears. The behavior of pyocyanus on potato differs widely in cultures from various sources, probably in keeping with the variations in pigment-forming. Whether the nonchromogenic bacilli, now associated with this group on general morphologic and biologic grounds, have suffered loss or suppression of a former pigment-forming capacity is not certain, though from what is seen under artificial conditions it is quite probable that they are varieties.

Morbid Effects; Toxins; Agglutination.—These bacilli were first found in the blue or green pus of wounds or the pigmented bandages soaked with wound secretions, the color in both cases being elaborated by the pyocyanus bacilli. In wound infections these bacilli are sometimes found, usually mixed with the commoner pus micro-organisms. They have also been found in various other local pathologic conditions, some of which apparently were solely due to their pathogenic activities. Thus they appear in purulent middle-ear disease, in suppuration in the cranial sinuses and meninges, in angina, bronchitis, bronchopneumonia, pleurisy, pericarditis and endocarditis, esophagitis, enteritis, metritis, appendicitis and peritonitis, synovitis, ureteritis, and pyelonephritis. A form of septicemia, sometimes with hemorrhages and with peculiar vesicular, papular, or bullous skin eruptions, also follows infection with this organism. Besides these more acute forms of infection, there is evidence to show that chronic infections and intoxications may also be induced by these bacilli. From the array of acute diseases above cited, it is evident that inflammation and suppuration are a frequent consequence of local pyocyanus infection. In the mucosa of the alimentary tract, inflammation may also be induced, with swelling of the lymphoid follicles, submucous hemorrhages, and finally necrosis of various stages, from superficial erosion to deep ulceration. Pyocyanus ulcers, situated as they frequently are in the lower ileum and accompanied by swelling or even supuration of the contiguous mesenteric nodes, present an anatomic picture closely simulating typhoid fever. Hemorrhagic inflammation and necrosis are also produced in the mucosa of the genito-urinary tract. In the acute general pyocyanus infections the lesions are splenic tumor, with the usual macroscopic evidences of congestion, and parenchymatous degeneration of the other viscera. Microscopically, parenchymatous lesions of the heart, liver, spleen, and kidneys, focal hemorrhages, and focal necroses, especially in the liver, are encountered. Chronic pyocyanus intoxication exerts its deleterious effect principally on the central nervous system, and experimental reproduction of this affection results in the formation of hemorrhagic foci in various parts of the brain, together with myelitis and neuritis.

Experimental inoculation of laboratory animals varies considerably in its results, according to the virulence of the particular race of pyocyanus bacilli employed. In successful cases subcutaneous injections of fresh cultures in guinea-pigs or rabbits produce spreading edema, inflammation, and suppuration, followed by general infection and death; intraperitoneal injections are more rapidly and certainly fatal, generally causing suppurative peritonitis.

Clinical evidence in the case of human beings, and experimental studies, point to the action of a toxin to explain the phenomena of pyocyanus infection. This toxin has not been definitely isolated, but appears to be intimately united with the bacterial cell. Injections of the bacilli killed by appropriate means cause intoxication in susceptible animals, and by

graduated dosage an immunity may be induced. The blood-serum of such immunized animals possesses active agglutinating properties when brought in contact with fluid suspensions of motile bacilli. The blood-serum of spontaneously infected human beings also produces agglutination, although the reaction is still too uncertain for clinical application. Antitoxic substances are produced in the blood-serum of pyocyaneus-immune animals, and such an antipyocyanic serum has been advised for practical therapeutic use.

The Bacillus of Influenza.—Richard Pfeiffer's announcement in 1893 of the discovery of the specific exciting agent in influenza, and the thorough studies recorded in his report, have been generally credited, and little disposition is manifested at the present time to doubt the correctness of his conclusions, although here again we have a case in which positive evidence from the standpoint of experimental reproduction of the typical disease has not been satisfactorily obtained. Pfeiffer's organism is a short, plump bacillus, found chiefly in the purulent secretion from the respiratory tract in influenza. It grows sluggishly in the laboratory, requiring a special

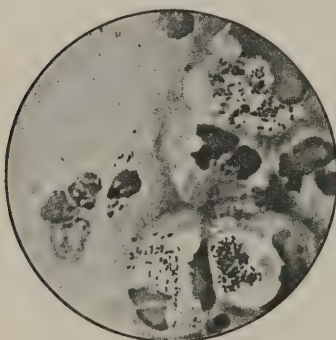


FIG. 85.—Bacillus of influenza: cover-glass preparation of sputum from a case of influenza, showing the bacilli in leukocytes; highly magnified (Pfeiffer).

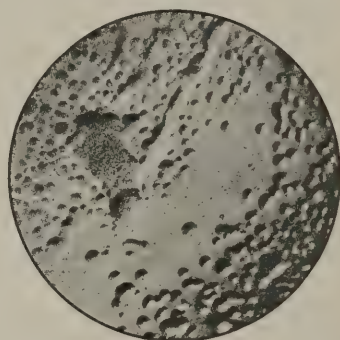


FIG. 86.—Bacillus of influenza: colonies on blood agar-agar; low magnifying power (Pfeiffer).

culture soil, prepared by smearing sterile blood or semen on the surface of ordinary nutrient agar. Upon yolk of egg, cultures may also be obtained. The influenza bacillus is not subject to a wide range of morphologic variation; and the restricted character of the artificial media upon which it grows, and its early death upon these media, make it difficult to determine its physiologic characteristics and variations. It must quickly find its way from one warm-blooded host to another, or perish; and the opinion is generally accepted that influenza is directly contagious through the medium of the infected respiratory discharges. Possibly an intermediate animal host may serve to harbor the bacterium and to transmit it to the human being, although no positive evidence in support of this assumption has been obtained. The difficulty of producing infection in the laboratory mammals by inoculating them in various ways with influenza cultures is also against this view. By resorting to intracerebral injections of living bacteria, Cantani has lately succeeded in producing a fatal form of influenza in rabbits, with marked symptoms of nervous irritability; and, contrary to the usual result of inoculations, the specific bacteria were found not only increased in

the local seat of infection, but present in the circulating blood and in remote organs, both microscopically and by cultures. About the injection-site was a gelatinous edema with numerous bacilli, the meninges were hyperemic and contained a serohemorrhagic transudate, the brain-substance was injected, and in the ventricles there was a purulent exudate. The peritoneal cavity contained an inflammatory exudate, the spleen was swollen, the adrenals and lungs congested, the liver hyperemic and in a state of fatty degeneration, and the kidneys well advanced in parenchymatous change. But in general the effects produced in man by this organism are such as to suggest an intoxication rather than a generalized infection.

Morbid Effects; Toxic Products; Immunity.—The principal anatomic alterations of influenza are found in the respiratory tract, a hyperemia and inflammatory reaction of the mucosa appearing in the larynx, trachea, and bronchi. Of especial significance is the pneumonia, which is the most frequent complication of influenza. This may take the type of a lobar or croupous pneumonia with an abundant fibrinous exudate, quite like the lobar pneumonia following a pneumococcus infection. In other cases the exudate is poor in fibrin and richly cellular, and accessory foci of lobular pneumonia are to be found with the lobar affection. The purely catarrhal or lobular form of pneumonia is also frequent. It is not rare for the acute pulmonary process to be followed by an interstitial, indurative inflammation taking a chronic course. Pleuritis, especially of a fibrinous character, often complicates the pneumonia; and abscess, localized necrosis, and extensive gangrene are not infrequent terminations. As marking the systemic effect of the infection, a swollen spleen is commonly encountered. Generally the kidneys and bowels show little evidence of disease, though there is a so-called "intestinal" influenza running a clinical course somewhat like typhoid fever and marked by a catarrh of the intestines and an enlarged spleen. Among the serous membranes attacked are the cerebral and spinal meninges, and the inflammation may take a serous, seropurulent, or suppurative form. The pleura, pericardium, and even the endocardium are liable to infection from the organism of influenza. The nasal and pharyngeal mucosa are often involved, from which such complications as middle-ear disease and sinus inflammations sometimes follow. Secondary or mixed infections with other pathogenic micro-organisms at times complicate the course of pulmonary influenza, and tuberculosis is not rarely a terminal consequence of this disease.

That an intoxication of some sort must result from the localized action of the influenza bacterium on the respiratory mucosa seems highly probable from the natural history of the infection in man, where such symptoms as profound weakness and evidences of nervous exhaustion appear, quite out of keeping with the local lesions. It appears, in fact, that the poison produced in consequence of influenza has a selective effect on the central nervous system, both from the preponderance of symptoms pointing to disturbance in the brain and spinal cord, and from the results of intracerebral injections of cultures of the influenza bacterium. Both living and dead micro-organisms produce symptoms of experimental toxemia in the nervous system, which has led Pfeiffer to conclude that the specific toxin is closely combined with the protoplasm of the bacterial cell. Attempts to isolate the influenza poison have thus far been negative.

In influenza there is little to be hoped for in the way of an artificial or

passive immunity. A previous attack of the disease confers but a transient immunity or none at all. Certain individuals are evidently strongly predisposed to the infection, while others enjoy a partial or complete immunity. Efforts to induce experimental immunity in laboratory animals have also been of little avail, and no one has succeeded in producing a protective or curative serum for influenza.

The Bacillus of Plague.—It is conceded with remarkable unanimity that the bacillus discovered by Yersin and Kitasato in 1894 (*Bacillus pestis*) is the causative agent of plague in all its forms. The organism is a rather thick bacillus, appearing usually as a short, plump rod. Its morphologic variation is not extensive, if we except the irregular and even branching forms produced on saline agar; while motility, noncharacteristic growth on ordinary media, negative proteolytic function, and active pathogenicity are remarkably constant attributes in bacilli from various sources and different parts of the world. It is the last-named attribute, pathogenicity, that especially marks the pest bacillus as a specific micro-organism.

Bubonic plague is essentially a disease of filth and poor hygiene. The specific bacillus often, if not invariably, chooses the rat (and possibly the mouse) as an intermediate host, infection being carried from rat to rat, and from rat to man under similar unsanitary conditions. It is further suspected that another animal of uncleanly surroundings, the flea, may transport the bacilli from rat to rat, and from rats to human beings. While this method of transfer is by no means improbable, the facts that the urine and feces of plague-stricken rats contain the bacilli, and that the dead bodies of infected rats also swarm with the organism, seem well-nigh sufficient to explain the spread of the disease. Flies also, perhaps, carry the bacilli. The appearance of the disease in the rodents before and during epidemics among human beings has been repeatedly confirmed, and it seems reasonable to credit the distribution of the malady primarily to the rat. But little has been ascertained as to the purely saprophytic habits of the pest bacillus, although it is claimed that organisms similar to it have been found in the soil.

Uncleanly habits and careless exposure of the skin to infection account for the majority of cases of bubonic plague in man. The bare feet and legs of male natives in India, China, and other eastern countries where plague is epidemic offer a ready portal for entry of the bacillus, and in women the unprotected hands and arms. Although the skin marks the point of introduction of the disease in most cases, inhalation infection occurs, and infection by swallowing is by some considered possible. All of these routes may be successfully employed in experimental plague, particularly in the rat, which may be infected by feeding it with the flesh of diseased animals or by cultures introduced in various ways.

Morbid Effects.—Human beings spontaneously infected with plague show one of three types of the disease: the bubonic, pneumonic, or septicemic. In the majority of cases the bubonic type develops, characterized in the severe form, as its name indicates, by buboes or swollen and discharging lymph-nodes. Here the infection atrium is generally the skin, in which a local lesion like a carbuncle may mark the exact spot of first attack. From the point of entrance in the skin the infection travels to the surrounding region, which responds by rapid swelling and sometimes by hemorrhagic edema of the connective tissues. From the group of glands first attacked the disease spreads to other superficial nodes, so that the glands of the entire

body, both superficial and deep (including the bronchial and mesenteric nodes), often enlarge. In the superficial glands, especially those adjacent to the primary focus, softening and the discharge of a puriform fluid often occur. In the pneumonic type, as the name indicates, the chief gross lesion is a broncho-pneumonia evidently due to aerial infection; while in the septicemic type the bacilli rapidly invade the blood from the primary focus, with only moderate involvement of the lymph-glands. There is a mild lymphatic variety of the plague; but except for this, taking any of the three types mentioned, the disease is generally fatal.

Aside from the swollen and often softened and necrotic superficial lymph-glands and the generally enlarged lymph-nodes, usually showing hemorrhagic foci on section, the morbid anatomy of plague is quite variable. Hemorrhagic ecchymoses in the skin, and submucous and subserous hemorrhagic areas are common. The spleen is swollen, soft, and contains macroscopic or microscopic hemorrhages. The kidneys show a moderate parenchymatous degeneration and are congested; the liver is somewhat swollen, and either pale or deeper red than normal. Hemorrhagic softening and superficial necrosis may be found in the stomach and intestines. Lobular pneumonia may be present, even in the bubonic type of the disease, and serofibrinous or purulent meningitis has been observed. In all the affected organs the pest bacilli are easily found, particularly in the blood-vessels.

Histologically the most important alterations are in the lymph-glands, in which the blood-vessels are found engorged with corpuscles and the cells increased in the earlier stages. Both lymphoid and large, clear hyaline cells appear in the affected node, the latter evidently being phagocytes, from the uniformity with which they are found with bacilli in their substance. An unusual number of mast-cells has been observed in the diseased glands. In more advanced stages, diffuse necrosis of the cellular elements of the gland occurs, until almost the whole gland-substance becomes converted into a mass of cellular and nuclear detritus with hordes of bacilli. Indeed, the larger bulk of some of these swollen and disintegrated glands may be made up of pest bacilli. Both the blood-channels and lymph-channels in and about the affected gland contain numerous bacilli, sometimes making bacterial thrombi of considerable size. It is significant to note that comparatively few polymorphonuclear leukocytes are to be found in the bubo, even when the disintegration is extreme, so that the process cannot properly be regarded as a suppuration, but as having more resemblance to the softening of a tuberculous focus. The pneumonia of plague seems to show no special variation from an ordinary bronchopneumonia, and the histologic changes in other viscera have nothing distinctive.

Toxic Products; Agglutination; Immunity.—From the rapid and extensive necrosis affecting the cellular elements of the pest bubo, it seems reasonable to conclude that the infecting bacilli produce a toxic substance especially destructive to the cells in their neighborhood. That this is not a

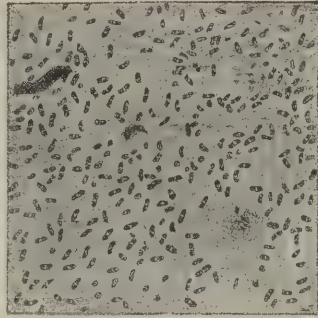


FIG. 87.—Bacillus of bubonic plague (Yersin).

diffusible toxin is probable from the absence of pronounced necrotic lesions in tissues and organs remote from the bacterial foci, though this must not be accepted as final, since some evidence seems to contradict it. However, no one has succeeded in separating a poison from the pest bacillus giving the specific effects of the living micro-organism, and it is therefore thought that the toxin, whatever its nature, is closely combined with the protoplasm of the bacterial cell, as is presumably the case with the organisms of typhoid fever and cholera.

A serum reaction may be obtained with fluid cultures of actively motile pest bacilli; but this agglutination test is unreliable for diagnostic purposes, both because of the difficulty in obtaining bacilli not already in clumps, and from the fact that only the serum of plague convalescents seems to contain the agglutinating substances.

It is claimed that a protective immunity of short duration may be produced in human beings by the injection of a vaccine consisting of a small dose of a fluid culture of the pest bacilli modified by heating to 70° C., and preserved by the addition of carbolic acid (Haffkine's prophylactic fluid). A serum said to possess specific antitoxic virtues has been prepared by injecting horses with increasing doses of living pest bacilli, and, while this antitoxic serum has no curative influence when the disease is established, its promoters assert that a small dose confers a protective immunity of some fifteen days' duration.

The Bacillus of Diphtheria.—There is no doubt that the so-called diphtheria bacillus of Klebs and Löffler is the specific cause of genuine diphtheria. Many of the clinical and pathologic features of the disease in man have been elucidated by laboratory experiments on animals. A special distinction pertaining to this micro-organism is that it has furnished a most brilliant and successful experimental demonstration of the mode by which it kills, and of a method of specific serum therapy applicable in medical practice.

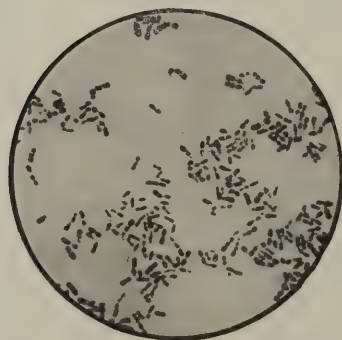


FIG. 88.—*Bacillus diphtheriae*, from a culture upon blood-serum. $\times 1000$ (Fränkel and Pfeiffer).

The shape and size of the organism of diphtheria is inconstant under varying conditions of natural and artificial growth. Sometimes it appears, both in the local lesion (the pseudomembrane in the throat) and on ordinary artificial culture media, as a short, plump rod. At other times it is long, straight or curved or bent, sometimes showing swollen, club-like, spindle-shaped, or even spheric ends. True dichotomy has also been noted, and several recent writers have removed the group of diphtheria organisms from the bacilli and have placed them among the branching, thread-like fungi. Bizarre branching forms appear both in sections of infected tissues and in cultures, being therefore no product of laboratory artifices, although the organism is susceptible to alterations in culture media, as shown by its property of producing shorter, thicker rods on glycerin agar than on Löffler's medium. Change from one animal species to another (guinea-pig to rat, for example) is capable

of altering the morphology strikingly. The physiologic characteristics, like the production of acid, the indol function, and the elaboration of toxic substances, are also variable. Hence a diversity in pathogenic action of these bacteria might be expected, and no doubt the failure to make allowance for these morphologic and physiologic variations has created many examples of the so-called "pseudodiphtheria bacilli."

To fix upon one characteristic as unalterable is difficult ; while recognizing the practical usefulness of special differential culture methods and of specific staining methods, like Roux's or Neisser's, in differentiating the true diphtheria organism from the pseudobacillus, the xerosis bacillus, etc., these reactions must not be regarded as specific in a biologic sense. The same may be said of the laboratory test for pathogenicity.

Morbid Effects.—The initial lesion wrought in man by the micro-organism of diphtheria is almost invariably an intense local inflammation, quickly followed by a membranous deposit. The favorite point of attack is the throat. We know nothing of the conditions that underlie such an attack, for a bacillus which laboratory tests show to be extremely virulent may reside on the pharyngeal mucous membranes of an entirely healthy person or produce only a slight local inflammation. Other and apparently less virulent examples may produce a rapidly fatal affection. Constitutional differences in the host are doubtless factors of great importance in determining the susceptibility to and effect of diphtheria, as is seen in the unfavorable prognosis of the malady and the inefficiency of specific serum treatment in victims having the lymphatic constitution. Previous or simultaneous infection with other pathogenic organisms is doubtless also an important matter. From these and other undetermined conditions a good deal of difference is shown, both in the local and systemic effect of diphtheria.

The manner of transportation of the infecting organism from host to host is not entirely clear ; for while much evidence points to direct transportation, other cases appear anomalous. How the organism passes its saprophytic existence is not known, although some observers have directed attention to milk, water, and even to flowers and plants, as intermediate carriers of diphtheria. Household pets, like cats and birds, occasionally harbor the diphtheria bacillus.

Aside from the throat and nose, the primary infection in diphtheria may occur in the mucous membrane of the eyes or of the genitals and in wounds of the skin. It is possible, too, that the organism may now and then gain access to the lungs, heart, or circulating blood, without the presence of a demonstrable external diphtheric lesion.

Its fibrinous structure is the most prominent characteristic of the localized diphtheric lesion. Following the inflammatory edema which ushers in the infection, comes the exudate or membrane which covers the mucosa more or less thickly. This membrane is white or grayish ; when sectioned, and examined with low powers in the fresh state, it shows several distinct layers : an outer grayish turbid one, a middle white glistening one, and an inner dark layer. All these zones are composed principally of fibrin in various states of aggregation, the central zone being compact, with less of the fibrillary components, and its glistening is due to a hyaline transformation to which the diphtheric exudate is particularly prone. Examined with high powers, and particularly after special staining for fibrin, the tangled threads

are seen making a network and becoming aggregated into more or less confluent masses or plates in the middle layer. Chinks or spaces are everywhere present in the membrane, although less abundant in the middle layer. Cells also abound in the fibrinous exudate, varying in different cases and in different stages in the same case; some present normal outlines, others show necrosis often reaching a stage in which only nuclei or nuclear fragments or chromatin dust remains. The early cellular elements are chiefly polynuclear leukocytes, afterward followed by mononuclear lymphocytes, and, in the deeper layers, by proliferated fixed-tissue cells. The behavior of the epithelial layer of the mucosa varies, sometimes remaining well preserved, again becoming disintegrated and contributing varying amounts of material to the membrane in the form of cast-off epithelial cells or aggregations of these cells. Fibrinous transformation may take place in the depths of the mucosa. The blood-vessels in the region are not only deeply injected, but often contain fibrinous thrombi. Curiously the lymphoid follicles of the infected mucous membrane seem to suffer little damage. In the superficial clear bounding layer of the membrane the diphtheria bacilli are found, often mixed with other bacteria.

In severe cases of the disease, most significant changes occur in regions remote from the primary seat; and while the specific micro-organisms may occasionally be transported by the circulation or find their way along the respiratory mucosa to the pulmonary parenchyma, still the deeper lesions cannot be ascribed to outwandering bacteria, but to the absorption of poisonous products generated *in situ* as a consequence of the original infection. In the more severe cases, the results of systemic affection are readily apparent in such anatomic changes as cloudy swelling and even fatty changes of organs, like the spleen, kidneys, heart, liver, and adrenals. More chronic cases of postdiphtheric intoxication show degeneration of the peripheral nerves; and, in both acute and chronic fatal diphtheria, changes in the ganglion-cells may be demonstrated by the Nissl method. While the faucial lymphoid follicles escape serious disturbance in the diphtheric process, more remote lymphatic glands are not so fortunate, as shown by the early swelling and uniform involvement in the cervical and other regions, and in the spleen. Histologically this swelling is accounted for largely by the presence of collections of endothelioid cells with large, oval, vesicular nuclei and a distinct nucleolus. These cells often occur in considerable areas in the splenic and intestinal lymph-follicles and mesenteric lymph-nodes. Many of them are hyaline, others well advanced in necrotic alterations. Inclusions of various kinds, like granules of necrotic protoplasm or of nuclear substance, or pigmentary masses giving the hemosiderin reaction, also appear in these large cells as the result of their phagocytic activity. But besides these lesions, diphtheria gives rise to a series of changes which, while by no means specific, are peculiarly the result of a general toxemia. These are the so-called *focal* or *insular necroses* which appear in the lymph-glands and certain viscera, the characteristics of which in diphtheria have been studied especially by Welch and Flexner. It is now known that these islands of necrosis occur in a number of different spontaneous infections, and that they may be experimentally reproduced by the injection of living bacteria and the poisonous products of bacterial activity, by the poisons of certain higher plants, the venom of poisonous serpents, foreign blood-serum, as the results of superficial burns, etc. The lesions may be reproduced in a typical manner in

animals by the injection of the poisonous products or toxins of the diphtheria bacillus.

Focal necrosis has been already described under *Necrosis* (see page 74), and its histologic features need not again be detailed; but it should be known that the mechanism of its production is not fully understood. Why, for example, the toxin should escape from the blood-vessels only in particular regions is not clear. In some instances the lesion can be shown, as Klebs has maintained, to be a minute infarction following the thrombotic or embolic occlusion of small blood-vessels. That such a process may occur in diphtheria is probable, since fibrinous metamorphosis is so pronounced a characteristic in the local infection and fibrinous thrombi are demonstrable in the blood-vessels of the pharyngeal mucosa and in more remote situations, especially in the blood-vessels and sinuses of the cervical lymph-glands, in the follicles of which deposits of fibrin also appear. The diphtheria toxin (and perhaps the other toxins concerned in focal necrosis) seems to have a peculiar property of elaborating fibrin-ferment, and the presence of this ferment in the circulation may be an important factor in favoring microscopic thrombosis and infarction. On the other hand, some of the foci are probably local tissue-reactions against the diffused toxin.

Diphtheria Antitoxin.—A temporary active immunity may be secured in susceptible animals by inoculation with living diphtheria bacilli at first attenuated by one of several methods, and later used in full virulence. But such a process is dangerous, unreliable, and unnecessary, since a more certain immunity may be secured by the use of the bacteria-free poisonous products of their growth, the *diphtheria toxin*, the chemical nature of which is not yet understood. In susceptible animals immunized by means of gradually increased doses of diphtheria toxin, an antidotal substance or antitoxin makes its appearance, chiefly in the blood-serum, which has the property of conferring a temporary immunity against diphtheria or of arresting the progress of the disease in the earlier stages. As to the nature of this antitoxin, we know nothing positive—it is not desirable to discuss here the elaborate theories advanced to account for it and to explain the *modus operandi* of its protective and curative action; but in diphtheria antitoxin we possess a therapeutic agent of great practical value. In actual practice this remedy is prepared from horse's serum, the animal having been immunized by increasing doses of a diphtheria toxin obtained by growing virulent bacilli in special bouillon until the height of toxin-production, when the organisms are filtered out, the filtrate being the toxin. The testing of the potency of the toxin by graduated dosage in guinea-pigs, and the testing of the antitoxic serum to determine its relative toxin-annulling property (described in *antitoxin units*) in the same animals, is one of the most interesting demonstrations of the biologic laboratory, giving much the same satisfaction as mathematic or physical elucidations.

The Organism of Human Tuberculosis.—Koch's bacillus of tuberculosis is a parasite which through evolution has practically reached the state of obligate parasitism. That it is a product of the evolution of a once saprophytic micro-organism may be surmised from what we know of other less advanced pathogenic species which are daily met in both saprophytic and parasitic existence. Quite recently additional evidence on this point has been obtained from two sources. By compelling the human tubercle bacillus to live for a time in the body of certain amphibia and also by

long-continued growth on modified artificial media, its biologic characters have been so changed as to permit its cultivation on ordinary culture media at the ordinary room temperature, and at a rate of growth considerably in excess of that seen in the unmodified organism grown on special media at the thermostat temperature. That is to say, it is possible by this artificial means to restore to this highly developed parasitic species certain of the more hardy characteristics, which probably were lost through long adaptation to a parasitic existence in warm-blooded animals. Confirmation also comes through the discovery of a series of bacterial organisms morphologically allied to the tubercle bacillus, but departing from it in sundry physiologic characters. To this class belong the butter bacilli of Rabinowitch and others, the timothy, dung, and grass bacilli of Möller, and the bacillus from the crypts of the tonsils, described by Marzinowsky. Possibly, too, the bacilli of avian and bovine tuberculosis are distinct species, although their

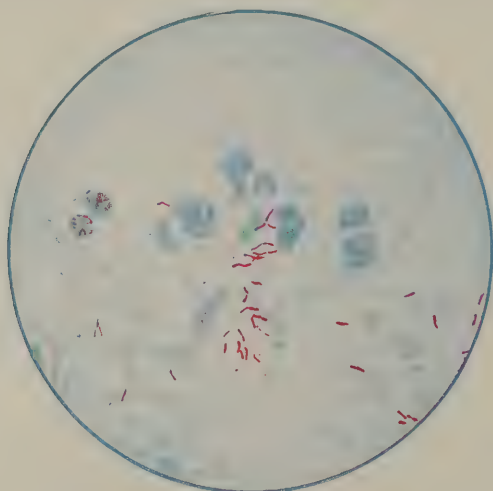


FIG. 89.—*Bacillus tuberculosis* in sputum, stained with carbolic fuchsin and aqueous methylene blue. $\times 1000$.

close morphologic and physiologic resemblance makes it probable that they are but varieties of the same group to which the typical bacillus of mammalian tuberculosis belongs.

In shape the bacillus is a slender rod, slightly curved, growing slowly at or near a temperature of 37.5°C ., and requiring special media for its artificial propagation. It reproduces in susceptible mammals a pathologic process running a definite course, with certain peculiar gross and minute lesions, closely resembling the tuberculous disease seen in man.

As to its morphology, the principal interest now hinges about the question of branching in the tubercle bacillus. There are those who claim that all branching forms of bacteria found in or obtained from tuberculous lesions or material, resembling Koch's bacillus in tinctorial and cultural peculiarities, are to be separately classed, and that the typical organism never shows dichotomy. But by experimental efforts, such as the intra-arterial or subdural injection of nonbranching tubercle bacilli, branching forms have been

produced. This evidence, taken with the intimate approach to the typical physiologic conditions of those branching forms spontaneously encountered in human tuberculosis, makes it highly probable that dichotomy is one of the characteristics of the tubercle-bacillus family, only temporarily lost in the most highly differentiated members. This phenomenon, which may be looked upon as a reversion, is also encountered in certain members of the tubercle-bacillus group growing spontaneously in the human organism, as shown at times in sections of tuberculous organs or in tuberculous sputum. Both under natural and experimental conditions, the tubercle bacillus sometimes goes beyond the condition of simple dichotomy to the formation of threads, thread-like masses, and radially arranged groups with clubbed ends, making an organism the morphology of which is similar to that of the ray fungi, as seen in actinomycosis. Indeed, from such morphologic and physiologic considerations as have been here outlined, systematic writers now generally incline to place the bacillus of human tuberculosis in the family of ray fungi of which actinomyces is the type, with affinities suggesting relationship both to the bacteria and to the moulds. In this light, the name bacillus as given to the organism of human tuberculosis is misapplied, although it seems expedient to retain it until the exact botanic position of it and its allies is better determined.

A practical point of considerable importance concerns the staining peculiarities of the tubercle bacillus and its related forms. The well-known acid-proof and alcohol-resisting property of this organism, when stained by certain anilin dyes according to the method of Ehrlich and Koch and its modifications, can no longer be regarded as specific for the typical tubercle bacillus, for such organisms as the butter, timothy, tonsillar, and grass bacilli give identical tinctorial reactions; and even the differentiation by staining reactions of the smegma bacillus, the so-called syphilis bacillus, and leprosy bacillus is far from satisfactory. There seems to be a large group of bacteria, including those just mentioned, into the composition of which fat-like substances enter, rendering them resistant to acids and alcohol after coloration with certain anilin dyes, and the bacillus of human tuberculosis is only one member of this group. This consideration must of course affect our interpretation of such a diagnostic measure as the staining for the tubercle bacillus in sputum, exudates, and tissues, although, as we shall see, some of the less characteristic members of the tubercle-bacillus group simulate the typical tubercle-bacillus, even to the extent of producing a disease the pathologic features of which are much like those of genuine tuberculosis. At any rate, this evidence all goes to strengthen the theory of the former saprophytism of the typical tubercle bacillus, at the same time indicating the possibility that some forms of tuberculous disease may be caused by organisms of this group, which are still capable of saprophytic existence.

Morbid Effects.—The reaction of the human organism to infection with

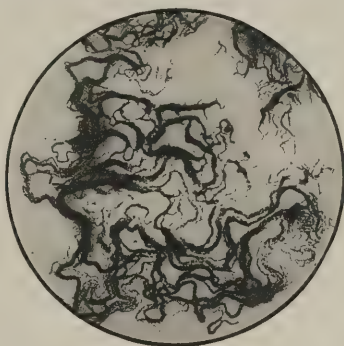


FIG. 90.—*Bacillus tuberculosis*: cover-glass preparation from a fourteen-day-old blood-serum culture. $\times 100$ (Fränkel and Pfeiffer).

the bacillus of tuberculosis presents a tolerably uniform picture. The principal lesion, and the one through which the name of the disease was assigned long in advance of the discovery of the specific parasite, is the familiar, translucent, grayish, millet-seed-sized nodule, the *tubercle*. As presented in miliary eruptions on freshly invaded surfaces, the macroscopic appearance of the tubercle is quite distinctive. In more ancient lesions, or in those in which extensive coalescence and exudation have occurred, the anatomic picture is less characteristic, although careful examination will usually disclose the individual tubercles. Anatomically, all gradations of the disease are to be seen, from the discrete, widely scattered miliary tubercles to immense degenerating pyogenic sacs representing destroyed areas. The gross picture varies not only according to the chronicity of the disease and the associated infections, but also according to the organ or tissues involved, there being marked difference in the behavior of cutaneous, osseous, lymphadenoid, serous, pulmonary, and cerebral tuberculosis, for example. The favorable outcome of a tuberculous process in the form of latent calcified foci, indurated foci, and even by connective-tissue repair, is a common sight at autopsy.

Histologically, tuberculosis is most often manifested by the collection of newly formed cellular elements constituting the tubercle, although it is important to recall that a diffuse cellular proliferation or a cellulofibrinous exudate may also mark the site of a tuberculous infection, with no histologic evidence of the tubercle proper. Following the usual description, the cellular elements of the tubercle may be divided into three classes: the *giant cells*, the *endothelioid* or *epithelioid cells*, and the *lymphocytes*. A reticulum, to some extent suggesting that of a lymph-gland, is at times present, and fibrin may also be found mingled with the cells. In early tubercles the blood-vascular channels are present, but their endothelial elements are soon stimulated into proliferative activity, and as the tubercle advances, especially in the more chronic and diffuse processes, the blood-vessels become occluded from endovascular inflammatory reactions or by thrombosis, this plugging of the vessels constituting one of the factors leading to the termination of tuberculous new formations—necrosis and caseation.

It was once thought that the giant cells of tuberculosis were peculiar to this disease, and that it was possible to distinguish tuberculosis by the peculiar features of the multinuclear cells of the tubercle. Such is not the case, since these cells offer no characteristic by which they may positively be distinguished from the giant cells of other granulomas, like syphilis, or from the foreign-body giant cells, whether under aseptic or infective conditions. The presence of demonstrable tubercle bacilli in the giant cells is distinctive, and possibly the calcareous or iron-containing masses thought by some observers to represent destroyed tubercle bacilli are also peculiar to this infection. The early necrosis of the giant cell of tuberculosis is suggestive, to be sure, but this outcome is by no means invariable. There is, indeed, a marked tendency to consider that this cell is not necrobiotic from its outset, the growing belief being that the giant cell is a defensive active product of tissue-reaction, and that it is phagocytic and reparative in function. The exact tissue-elements from which the giant cells arise—whether mesoblastic or epiblastic, or both—is not determined; nor is the mode of formation, whether by coalescence of small cells or by nuclear division and growth,

definitely ascertained. Similarly, the fate of these structures in healed tuberculosis is not clear, although a separation into small living cells, as suggested by Hektoen, is probable.

In like manner the origin or source of the endothelioid and lymphoid cells of the tubercle is not well settled, although analogy points to the endothelioid cells as springing chiefly from the fixed mesodermic tissue-elements (endothelial and connective-tissue cells), and the lymphoid from the blood, lymph-nodes, and possibly from the lymph-spaces. Whether the lymphoid and endothelioid cells are in any way related is unknown, although by some they are regarded as developmental phases of a common cellular element. The lymphoid cells in recent tubercles are poor in protoplasm, like those found in early inflammatory conditions generally; but in the more chronic tuberculous lesions the plasma-cell appears, with its more abundant basophilic protoplasm, whether by metamorphosis of the lymphocyte or otherwise is undetermined. The mast-cell may also make its appearance in the connective tissue about chronic tuberculous lesions. Like the giant cell, the endothelioid and lymphoid cells of the tubercle are not specific of tissue-reaction to the tubercle bacillus. More careful histologic study is demonstrating the extensive formation of endothelioid cells, both diffuse and focal, in a number of infections, like typhoid fever, diphtheria, scarlet fever, and pneumonia, while the lymphoid cell is common to inflammations generally. A still closer resemblance to the simpler infections is seen in caseous tuberculous pneumonia, in which exudation is quite as marked as proliferation, in rare cases even taking the characteristics of an ordinary purulent exudation. The same may be said of the fibrinous exudation, the thrombosis, and the endarteritis sometimes occurring in tuberculosis. Moreover, the necrotic changes, ranging from cloudy swelling of the giant cell and microscopic focal necroses to advanced caseous metamorphosis, are the same as in other morbid conditions. Histologically, tuberculosis is not to be distinguished by the peculiarity of any of the elements of the tubercle, but especially by the arrangement of the several proliferative elements—giant cells, endothelioid and lymphoid cells—into a focus, the sum of which is the tubercle. As, however, our knowledge of pseudotuberculosis is increasing, and with further light on the bacteria allied to the bacillus of Koch, we find that none of these histologic criteria is sufficient to stamp the process as tuberculosis without the concomitant identification of the typical tubercle bacillus. Thus the bacilli from butter produce in the guinea-pig a morbid process running an identical course with experimental tuberculosis, accompanied with macroscopic tubercles, and differing only in its more exudative nature (polynuclear leukocytes, fibrin, etc.) and the absence of giant cells, though lymphoid and endothelioid cells are proliferated. The timothy, dung, and grass bacilli produce a milary tuberculosis in guinea-pigs, with gross and microscopic resemblance to the disease produced by Koch's bacillus.

Infection by the typical organism of tuberculosis is, according to our present ideas, only possible through the direct route from host to host, without intermediate saprophytic existence. All experimental evidence indicates that the tubercle bacillus has a considerable longevity outside of the animal body, under certain conditions, but with no power to reproduce until again implanted in suitable living animals. In man the infection occurs most commonly through the respiratory tract, probably not so much by the

inhalation of dried tuberculous material, as was formerly imagined, as from the bacilli-laden mist expelled during the coughing of consumptives. The large proportion of latent tuberculous bronchial-gland infections revealed by careful postmortem analysis of these organs shows how common this mode of inhalation infection is. Sometimes the lower respiratory tracts are spared, the invasion taking place through the nasopharyngeal surfaces, by way of adenoid tissue, like the tonsils, to reach the cervical lymph-glands. Infections by the digestive tract anywhere from the esophagus to the rectum, by the genito-urinary tract, through the nipples, by traumatism through the skin, are also possible, though more rare; these regions, and especially the bowels, are more often subjected to secondary infection. How far milk and meat of tuberculous animals are to be held accountable for intestinal tuberculosis is an unsettled question. Probably we shall also learn that transmission of infective material by insects, such as flies, is an important agent in spreading tuberculosis.

From the primary focus, infective material may be transported by the lymph-channels, blood-vessels, and by contiguous surfaces like serous membranes. The swallowing of expectoration from tuberculous lungs, especially in children and feeble-minded adults, is a frequent cause of gastro-intestinal infection. Erosion into the blood-vessels, with direct penetration of material containing the tubercle bacillus, or the production of infected thrombi and subsequent embolism, should always be sought for in sudden generalized eruptions of milary tubercles.

Toxic Products; Immunity; Agglutination.—The tubercle bacillus elaborates poisonous substances during its biologic activity, but their nature and the part they play in producing disease are little understood. Artificially a poisonous mixture, with the peculiar specific effect of causing a characteristic febrile reaction in tuberculous animals, may be obtained; this is the *tuberculin* of Koch and its various modifications. These products have not proved to be of so much practical value as therapeutic agents as once proclaimed, although their employment for diagnostic purposes is still in vogue with human beings and on a large and seemingly successful scale for detecting tuberculosis in cattle. Despite extensive patient efforts, a useful antitoxic serum for tuberculosis has not been produced.

By growing tubercle bacilli in suitable liquid media with regular agitation for prolonged periods, it seems possible finally to separate the individual organisms and to induce a kind of motility, presumably an exaggerated form of molecular motion. Such cultures are now employed in performing an agglutination or serum test, with results indicating its value as a diagnostic measure, although the technic is so complicated and the results so meager that the method can only be looked upon as in the stage of experimental evolution.

The Bacillus of Syphilis.—There is not sufficient evidence at hand definitely to pronounce the bacillus of Lustgarten the specific cause of syphilis, although a strong tendency in this direction is manifested by those who have most carefully studied the subject. Should it eventually be ascertained that this micro-organism is the exciting cause of syphilis, then we will have another example of a highly evolved parasite comparable with the bacillus of leprosy.

The organism in question, which has been repeatedly found in primary, secondary, and tertiary syphilitic lesions, bears a close morphologic resem-

blance to *Bacillus tuberculosis*. Moreover, it belongs to the acid-proof and alcohol-proof class of bacteria, its property of retaining anilin dyes after moderate application of acids and alcohol making it possible to differentiate it in syphilitic tissues and secretions. Both in its morphology and staining reaction, Lustgarten's bacillus resembles the smegma bacillus, and several authorities claim that the syphilis bacillus is in reality nothing more than the latter organism. Specific staining tests have been devised for identifying these two bacilli, depending principally on the feeble alcohol-resisting power of the smegma bacillus as compared with the rather weak acid-resisting tendency of the syphilis bacillus. More reliance should, however, be placed on cultivation experiments, since it has been found possible to grow the smegma bacillus on artificial media, which has not been accomplished with that of syphilis. Typical tubercle bacilli are more acid-resisting than Lustgarten's bacillus, and can also be cultivated and inoculated into animals for differential purposes; and the leprosy bacillus, which has some points of similarity, is much more abundant in the morbid tissues and resists the action of strong acids to a high degree.

The contagium of syphilis is transmitted directly from one human organism to another. There is no authentic instance of indirect or intermediate transmission, and repeated efforts to inoculate other mammals have failed (Ravenel), the reputed successful cases proving to be instances of tuberculous or septic infection and not analogous with syphilis as seen in man. There is abundant evidence of the direct infection of the fetus *in utero*, both through the male and female sexual elements at conception, or later through the mother.

Syphilitic infection manifests itself by primarily local and later a general tissue-reaction tending to assume much the same microscopic granulomatous structure seen in tuberculosis and leprosy. It is remarkable for the extreme variation presented in the gross anatomic lesions as to size, color, consistency, and extent. With Virchow, we may distinguish two forms of tissue-change, the inflammatory hyperplastic and the gummatous or neoplastic degenerative. At the point of entry of the specific irritant a localized proliferation of connective-tissue elements, lymphoid, endothelioid, and sometimes giant cells, takes place. Being confined to a limited area, these proliferated elements produce a firm or indurated condition characteristic of the *initial sclerosis* or *chancre*. Necrosis and liquefaction of the tightly packed cellular elements lead to ulceration of the central portion of the indurated area, producing the familiar hard chancre of syphilis. Both in the primary lesion and in the subsequent manifestations of the chronic inflammatory reaction of syphilis, the lymphoid cells gradually become replaced by numerous elements giving the staining reaction of plasma-cells, and later fibroblasts appear, particularly in regions where protective granulation-tissue is forming as a barrier to the progress of the specific affection or in the healing process. Here, in the chronic lesions, mast-cells are also abundant. Like other allied infections, syphilis seems to irritate principally the elements of the connective tissue, and in consequence we find in both early and later lesions a proliferation of endothelioid cells, small round (lymphoid) cells, and giant cells. As in most other infections, the endothelioid cells, giant cells, and certain migrated leukocytes engage in phagocytic activity in the effort to rid the body of noxious invaders or to remove the detritus of cellular necrosis.

A gradual degeneration of the more or less localized nodular gumma,

ending in necrosis and caseation, is seen in the tertiary lesion. How much of this necrotic process is to be charged to the direct destructive effects of a syphilitic poison and how much to circulatory disturbance is not clear, although the latter factor must play a prominent part, since obliterative changes are extremely common in the blood-vessels of syphilitics. Sometimes the syphilitic affection is manifested only by a fibrous-tissue overgrowth throughout an organ like the lung or liver.

Syphilis seems also to stand in relation to certain diseases of the nervous system, particularly posterior sclerosis (locomotor ataxia) and meningo-encephalitis (general paralysis of the insane). The changes in those diseases are not specific, and bear no resemblance to the ordinary syphilitic lesions; hence they are sometimes called *parasyphilitic* lesions.

The Bacillus of Leprosy.—If we are to judge from culture experiments, then the bacillus of leprosy, which has never been grown successfully on artificial media, is more markedly an obligative parasite than the bacillus of tuberculosis. Morphologically it resembles the latter, and, now that attention is being directed to the affinities of the tubercle bacillus with the ray fungi, it is pertinent to recall that Babes some time ago noted a branching and radial arrangement of the leprosy bacillus resembling that seen in actinomycosis. Another point of resemblance is the strong acid-resisting property of the stained leprosy bacillus, a property in which it surpasses the most pronounced examples of this group of bacteria. Nothing is known as to the life history of the organism outside its human host; even the question of its contagiousness is disputed, although a direct transfer by contagion seems highly probable in view of the advanced parasitic adaptation of the leprosy bacillus—if it be really the specific causative agent—a conclusion in which opinion is almost unanimous even in the face of negative experimental evidence.

The usual morbid process with which the leprosy bacilli are associated is a chronic proliferative reaction, producing a granuloma somewhat like that seen in tuberculosis, actinomycosis, syphilis, and glanders. Its course is generally more chronic than any of these infections, and this is the more surprising in view of the immense numbers of bacilli concerned in the

disease. The new tissue consists of richly cellular nodules or smaller foci with a fibrillary and vascular ground-substance. Most of the new cells are of an endothelioid nature, some being extremely large and at times vacuolated. Multinuclear giant cells also abound in the proliferated tissue. Vast numbers of the bacilli appear in the spaces of the leprous granulation-tissue and also in the cells, sometimes lying in vacuoles, again crowding the cytoplasm so extensively as to leave no trace of cell or nuclear structure visible. Necrosis of the individual cells in the morbid tissue occurs, although the degeneration is slow in advancing to

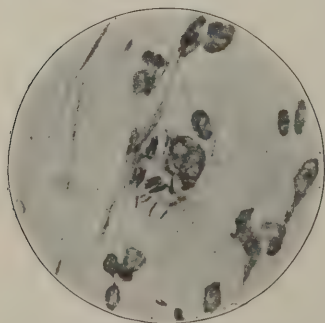


FIG. 91.—Leprosy bacilli in cutaneous cells.
× 1000 (Karg and Schmorl).

the stage of liquefaction and ulceration. Caseation is rarely present, and, in several of the cases in which it has been reported, it has been shown by animal inoculation experiments to be due to mixed infection with the tubercle bacillus.

The leprous affection is for the most part found in the skin and subcutaneous tissues. The nerves are usually affected in combination with the cutaneous disease, a proliferative and indurative lesion resulting from the invasion of the bacilli. A more generalized affection is also noted, in which the mucous membranes, cartilage, lymph-glands, and such viscera as the brain and spinal cord, liver, spleen, and testicles, are invaded by the bacilli, with the production of more or less proliferative reaction, nodular or diffuse. Secondary affections due to other causes also develop; they are principally due to secondary infection with the bacillus of tuberculosis. But leprosy bacilli have been found in the circulating blood. The close morphologic and tinctorial resemblance between leprosy, tubercle, and smegma bacilli makes it always difficult to distinguish these organisms, especially when in combination, as they sometimes are in leprosy. Careful animal experimentation should decide definitely between tuberculosis and leprosy, since the latter disease has never been artificially communicated to any of the laboratory animals.

The Organism of Glanders.—While having its ordinary parasitic habitat in the Equidæ (horses and donkeys), the bacillus of glanders sometimes infects human beings, producing a morbid process similar to that seen in horses. The parasite is generally a small slender bacillus, growing on ordinary culture media, but without striking biologic characteristics. More careful recent studies of its morphologic characteristics have shown that the slender bacillary form is not the only one, for in agar cultures it has been found to produce extensive networks of tangled threads; and the individual elements, when separated, show wide variation in size and shape, while side-branching and sometimes multiple one-sided branching are observed, together with the development of clubbed ends and other asymmetric forms. These characters indicate the propriety of considering the micro-organism of glanders as allied to the ray fungi. The longevity varies considerably, some stocks dying in a short time under ordinary conditions of moisture and temperature, others surviving prolonged drying. True spores have not been identified, and, with the exception of irregularities in staining, probably due chiefly to plasmolysis, little change in form appears. In the affected equine and human tissues, the bacilli are usually abundant, lying in compact groups or diffusely scattered. Nothing has been determined as to the life history of these micro-organisms outside of the animal body, and the source of the extraneous infection is not known. Having once gained a parasitic foothold, transmission from animal to animal seems to be comparatively easy, since the chosen regions (nose and respiratory tract or skin) are those from which infection readily occurs through the breath or respiratory discharges. In the comparatively rare cases in which man contracts the disease, direct contact with infectious discharges or tissues and inhalation of infectious mist are considered to be the usual modes; and, in conse-

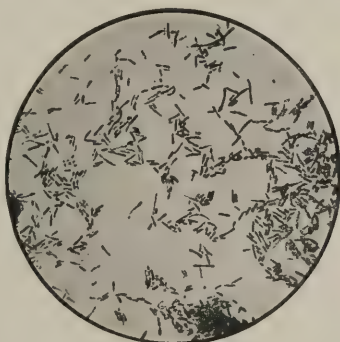


FIG. 92.—*Bacillus mallei*, from a culture upon glycerin agar-agar. $\times 1000$ (Fränkel and Pfeiffer).

quence, the starting-point is found in the conjunctiva, nasal mucosa, or the skin.

The effects of glanders infection in man are either acute or chronic. In the acute form the disease pursues a febrile course, like severe typhoid fever or a septic infection. In the cutaneous type a pustular eruption appears, the pustules discharging and leaving ulcers with dirty, ragged edges and purulent floors. A lymphangitis may proceed from the cutaneous foci, and an infiltration at times appears in the intermuscular connective tissue. Pulmonary embolic areas from the cutaneous lesions may occur, resembling pyemic foci, and the same process has been noted in the kidneys and myocardium. An aspiration-pneumonia of the lobular form at times follows glanders of the upper air-passages, the diseased areas remotely resembling tuberculous foci. They may terminate by softening and even by cavity-formation. The chronic form of human glanders is characterized by sluggish ulcers of the nasal, pharyngeal, tracheal, or bronchial mucosa, and by an induration of the cutaneous lesions. Abscesses may occur in the subcutaneous and intermuscular tissues, the exudate having a viscid, mucoid consistency. Caseous and even calcareous foci may also mark the site of chronic glanders, appearing in the lungs, bones, testes, and liver. The lymphatic glanders (farcy) seen in horses, or the more chronic nodular cutaneous farcy, is rare in man.

In the nasal mucosa the infection induces either a diffuse proliferation of lymphoid cells and endothelioid cells and migration of polynuclear leukocytes, or the proliferated cells may accumulate in groups, producing tubercle-like nodules. In the internal organs the process may be either a diffuse or a nodular one. The glanders lesions on the skin or mucous membranes tend to early necrosis, and the characteristic ulceration follows. In the viscera, necrosis is often accompanied by purulent infiltration and abscess-formation, or caseous metamorphosis ensues.

Straus's method of intravital diagnosis of glanders seems to give trustworthy practical results. It consists in the peritoneal inoculation of male guinea-pigs with suspensions of the suspected material (pus, infected tissues, etc.), a positive effect being marked by swelling of the testes as early as the second day, and by swelling and even ulceration of the scrotum by the sixth or seventh day. Autopsy shows the presence of glanders nodules in the spleen, omentum, and liver, and an inflammatory, purulent, and caseous infiltration of the tunica albuginea. A more elegant and useful method of diagnosis, of considerable practical utility in horses, is the *mallein test*, in which mallein (a glanders toxin obtained by growing glanders bacilli in fluid media and separating the organisms from their products by filtration) is injected into the susceptible animal, a positive effect being characterized, like that of the tuberculin test, by febrile reaction in four to ten hours and by edema at the site of injection.

While not capable of true motility, the bacilli of glanders, when separated in fluid cultures, possess a wide range of Brownian movement; and it has been found that agglutination may be produced by adding the blood-serum of infected horses to these fluid suspensions.

The Bacillus of Tetanus.—This sporogenic, anaerobic bacillus, identified in its saprophytic and laboratory characteristics by Nicolaier and Kitasato, is one of those pathogenic micro-organisms the causal relationship of which to the disease, tetanus, admits of exact experimental demonstration.

Abundant evidence shows that the bacillus ordinarily inhabits the superficial layers of the soil in company with several other pathogenic micro-organisms, and that it gains entrance to the human body or to that of a susceptible mammal either directly from the soil or from dirty objects. From the standpoint of parasitism, the bacillus of tetanus is a notable exception to the rule for pathogenic micro-organisms, being almost unadapted to multiply in the body of the host, and still capable of producing disease and almost certain death through the elaboration of an intensely virulent and rapidly diffusible poison. Its analogy is rather with the higher plants which elaborate poisonous products without being in any way parasitic, than with the class of parasitic micro-organisms to which it belongs. How such a poison-producing property should have been acquired in an organism not adapted to a parasitic existence is an interesting problem, only to be answered by a wider knowledge of the saprophytic life habits of the tetanus bacillus. In a state of Nature the organism is apparently a strict anaerobe; in its usual habitat, the soil, it fails to find oxygen-free conditions necessary for its vegetative existence, but it is provided with spores which, like those of the other anaerobic earth bacilli, are exceedingly resistant to ordinary destructive influences and have extraordinary longevity.

Access to the human organism is gained almost exclusively through wounds; and the clinical types of traumatic tetanus, tetanus of the newborn and of the puerperium, are explained in this way. Doubtless, too, most examples of the so-called idiopathic or rheumatic form of tetanus depend upon the infection of minute and hidden or healed wounds. Possibly the stings of certain insects may also be found at times to be instrumental in carrying the infectious material. But under certain conditions of association or symbiosis with other bacteria it appears that the tetanus bacillus may assume aerobic functions, and under such circumstances it may multiply in regions supplied with oxygen. Some cases of tetanus complicated with pneumonia seem explicable on this basis; the tetanus bacillus, in association with the diplococcus of pneumonia, growing in the oxygenated pulmonary tissues. It is also noteworthy that the tetanus bacillus is commonly associated with one or another of the pyogenic bacteria in wounds from which tetanus is acquired; and since some of these wounds seem to offer no opportunity for anaerobic vegetation, it is quite possible that here also the symbiosis may aid the organism of tetanus in multiplying under otherwise unfavorable conditions. That the tetanus bacillus, isolated in purity and grown under artificial anaerobic conditions, reproduces tetanus in experimental animals is unquestionable; but by injecting pure tetanus cultures into animal tissues we are establishing conditions not present in spontaneous tetanus, particularly that coming from extensive superficial wounds where mixed infection is invariably present. At any rate, the clinical phenomena of tetanus are to be ascribed not to the extensive invasion of the organism with the tetanus bacillus, but to the poison set free by its local activity.

Morbid Effects.—Except for the local wound which pursues the course

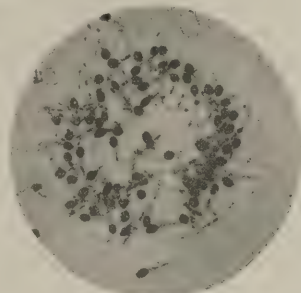


FIG. 93.—Bacillus of tetanus (spore formation). $\times 1000$ (Migula).

common to such lesions, and the clinical manifestations of tetanus, which need not be here discussed, the reaction to this micro-organism and its poison is remarkably devoid of demonstrable gross or microscopic changes. From clinical phenomena it is evident that the central nervous system especially suffers from the effects of the tetanus poison, although even the histologic alterations here are slight. Careful examination of material from the cerebrum and especially the medulla of fatal cases of tetanus, freshly obtained and properly treated, shows changes in the ganglion-cells, such as disintegration of the chromophilic bodies and displacement of the nucleus, similar to those noted in other intoxications.

Toxin ; Immunity ; Serum-therapy.—Both at the point of inoculation in susceptible animals and in artificial media, the tetanus bacillus elaborates a poisonous substance believed to be a proteid—a toxalbumin. This poison permeates the artificial fluid media, and may be obtained in solution by filtering off the bacilli. By certain chemical manipulations it has been precipitated out of these solutions in a more or less pure state. The filtrate as well as the precipitate (tetanus toxin) is poisonous for susceptible animals in doses extraordinarily minute, and reproduces physiologic reactions corresponding precisely to the train of symptoms manifested by animals spontaneously infected with the tetanus bacillus. The injection of these poisonous substances in a form much attenuated (generally obtained by treating the fluid filtrate of artificially grown tetanus bacilli with some chemical or by heat) is tolerated by susceptible animals ; and, by gradually increasing the dose after suitable intervals, an immunity against the potent poison, either in its artificial condition or as elaborated by the living tetanus bacilli, may be produced. Just as in the case of natural tetanus, so in that produced artificially by the injection of bacteria or their toxins, a certain time elapses before symptoms manifest themselves. The shorter this “period of incubation” in the human subject, the more serious is the disease. The blood-serum of immunized animals becomes antitoxic ; that is, capable of neutralizing, in some manner as yet imperfectly understood, the poison of the tetanus bacillus. For practical therapeutic purposes, this antitoxic serum (tetanus antitoxin) is generally prepared from an immunized horse, and offered in the liquid or dry form. That it is an antidote to the tetanus toxin is undoubted from the positive results of numerous animal experiments ; but spontaneous tetanus as encountered in the human being has generally made such headway when discovered, and so much poison has already been elaborated, that therapeutic success after injection of the tetanus antitoxin is uncertain. Still, upon the whole, the results are such as to prompt the general employment of this method. As a preventive agent in case of suspicious wound infections, the use of tetanus antitoxin is rational, since animal experimentation proves that a passive protective immunity against tetanus may be secured by relatively small doses of the antitoxin.

As the tetanus toxin is eliminated in the urine, the injection of urine from a case of the disease into a susceptible animal, *e. g.*, a white mouse, may be used as a test.

Bacillus Aerogenes Capsulatus.—This is an anaerobic, pathogenic bacillus, ordinarily passing a saprophytic existence in the soil. It appears to be a constant inhabitant of the intestines of man and other mammals, possibly finding its way there along with certain uncooked green vegetables more or less covered with particles of earth, which form a part of human diet.

From its moderate variations in morphology, and more especially from the irregularity of its spore formation, together with slight physiologic variations in organisms from different sources, it appears that several varieties of allied bacilli are included in this group. Moreover, since the property of capsule formation is not possessed by some members of the group, which agree with the type species in other particulars, the name "capsulatus" can hardly be regarded as appropriate for all the varieties. Its most constant attribute seems to be the gas-producing one, hence the desirability of the term "gas bacillus," by which the organism is now commonly known, as applied by Welch and Nuttall, who first accurately described it.

Ordinarily the gas bacilli appear as rather coarse, nonmotile rods, resembling anthrax bacilli in size; they grow in clumps, in pairs and short chains, rarely in filaments. Spores are uncommon in bacilli from the animal body, and may or may not form on artificial culture media, of which blood-serum seems most suitable. They are anaerobic, though not so strongly as the tetanus bacillus. Glucose, saccharose, and lactose are fermented, hydrogen especially being evolved. Fresh tissues containing the bacilli, or freshly isolated cultures from infected tissues, are pathogenic for guinea-pigs, pigeons, sparrows, and rabbits, producing gaseous edema and necrosis which often spread rapidly. A useful test for the organisms of this group, devised by Welch and Nuttall, consists in the intravenous injection of the bacilli into rabbits, which are killed after a few minutes. Gas is produced in the blood and organs, where the gas bacilli multiply actively after the death of the animal, and whence they can be readily isolated.

Morbid Effects.—Cadaveric decomposition, accompanied by the production of gas in the body, may almost invariably be ascribed to bacilli of this group. The same is true of the formation of gas bubbles in the blood and of gas cysts in the viscera, particularly the liver. In both cases the gas bacilli probably find their way most frequently from the intestinal canal, which, as has been remarked, often harbors them in the living animal. Often gaseous blood and emphysematous organs (the "Schaumorgane" of the Germans) appear in autopsies one hour after death; but here, as in most if not all of these cases, the phenomenon is to be ascribed to an agonal invasion of the blood by gas bacilli, by which they are distributed to various organs and tissues, to multiply rapidly after death. On microscopic examination of the tissues a zone of disintegration is usually found around the clear.

During life, the most important condition ascribed to the pathogenic activity of this class of organism is emphysematous gangrene, a serious form of wound infection. Here the gas bacilli are principally concerned, obtaining access from the exterior through filth of various kinds. An exudate of a hemorrhagic, edematous nature, with comparatively few leukocytes, appears, with gas bubbles about which necrosis of the tissue-elements and mechanic disorganization may be observed. This gaseous and necrotic edema spreads, sometimes involving extensively the subcutaneous tissues of the body. Infections may proceed from other points, as the uterine cavity, urinary tract, gastro-intestinal canal, biliary apparatus, and respiratory tract. A general visceral emphysema with gas bubbles is often found after infection by the external or internal routes; but how much of this is to be assigned to agonal and postmortem production is difficult to decide. In some cases emboli of liver, spleen, and bone-marrow cells have been found in remote parts, like the lungs. In some of the fatal cases of emphysematous gan-

grene, death is apparently caused by the absorption of toxic products generated by the gas bacilli, although the frequency of mixed wound infections makes it difficult to eliminate other factors.

Little is known concerning the toxins produced by this group of anaerobic bacteria, and no substantial knowledge has been obtained relative to natural and artificial immunity.

The Bacillus of Malignant Edema.—Still another anaerobic, spore-producing bacillus inhabiting the soil and appearing as one of the agents of cadaveric decomposition, and occasionally of a morbid condition in man, is the so-called bacillus of malignant edema, described by the French, since Pasteur's announcement in 1877, as the "*Vibrio septique*." There is a strong family likeness between this organism and the gas bacillus of Welch and Nuttall, and most European bacteriologists seem to include with the bacillus of malignant edema all allied anaerobes, among them those that produce gas in the tissues. The laboratory differential points between the two organisms are a slight difference in morphology; with motility, general spore-formation, more rapid peptogenic power and putrefaction,

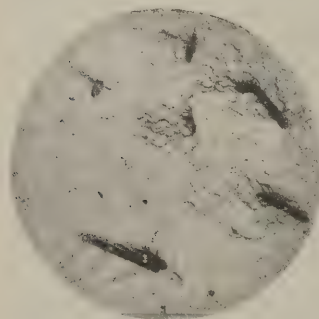


FIG. 94.—*Bacillus oedematis* (flagella).
× 1000 (Migula).

and lessened fermentative functions, as characteristics of the malignant edema bacillus. These features are hardly sufficient to be set up as specific, particularly since both organisms show considerable variation; and it seems highly probable that careful study will prove the bacillus of malignant edema and the gas bacillus to be simply varieties of a common anaerobic stock. The bacillus of malignant edema has been found in the intestinal canal of healthy animals.

The result of infection with this organism is a spreading bloody edema, appearing usually as a complication of wounds contaminated with dirt. Experimental malignant edema is readily produced in animals by subcutaneous inoculation with garden earth and similar material, showing that the usual saprophytic habitat of this organism is that common to the tetanus bacillus; indeed, a mixed infection of malignant edema and tetanus is at times seen in experimental cases and wound infections in man. Emphysematous gangrene and septicemia are also ascribed to the action of this organism, corresponding precisely to the effects produced by the gas bacillus, so that both the botanic position and pathologic bearings of the two bacilli are very confusing. Should specific differential characteristics be ultimately established between them, it is probable that the characteristic morbid effect will be found to be the absence of emphysema in the lesion produced by the malignant edema bacillus and its constant presence in organs and tissues invaded by the typical gas bacillus.

Bacillus Botulinus.—One of the indirect methods through which bacteria induce disease in animals is by the production of poisonous products in foodstuffs before these are ingested. Sometimes the foodstuff harbors both the living, active bacterium and the poisonous substances of its manufacture. The organism described as *Bacillus botulinus* is one of a group of anaerobic

bacilli, which act both directly and indirectly, producing in raw meat their toxic substances and also occasionally multiplying in the body of the infected individual.

This group of anaerobic bacilli somewhat resembles the malignant edema bacillus morphologically, although subject to considerable variation in size and shape; and it shows similar physiologic characteristics when subjected to the routine laboratory tests. They are motile, usually sporogenic, proteolytic, and gas-producing anaerobes. Thus far they have been found to induce disease only when contaminating uncooked or partly cooked meats; these meats show more or less evidence of putrefaction. The contamination is generally to be ascribed to prolonged sojourn of meat in dirty surroundings or to imperfect methods of preservation.

Morbid Effects.—The prominent symptoms of botulism in man are colic, vomiting, and diarrhea, usually followed by constipation. Evidences of profound disturbance of the nervous system, such as visual disorders and ptosis, appear in severe cases, followed by circulatory and respiratory irregularities, anuria or dysuria, aphonia, collapse, dyspneic attacks, and gradually weakening pulse in the fatal cases. Consciousness is intact almost to the last, delirium appearing only in the collapse. Drowsiness is often marked, and muscular palsies may appear. The gross changes at autopsy are not particularly prominent, a general visceral hyperemia and moderate parenchymatous degeneration, with punctiform hemorrhages in the brain, being most prominent. Microscopically the liver shows parenchymatous and fatty degeneration, with moderate emigration of leukocytes, while infarctions and fibrinous thrombi may be found in the kidneys, and a granular or fatty degeneration in the heart-muscle. The spleen is usually swollen and packed with red blood-cells, and phagocytosis may be abundant here as well as in the bone-marrow. In animals killed experimentally by contaminated meat or by the toxins of the bacilli, the changes above noted are found, together with a chromatolysis of the ganglion-cells in the nuclei of certain cranial nerves (hypoglossal, motor oculi, vagus) and of the Purkinje cells of the cerebellum. The blood-capillaries in these regions are choked, and hemorrhagic foci are frequent.

Poisonous Products; Immunity; Antitoxin.—Filtered infusions of contaminated meat, when administered by the mouth, produce the characteristic symptoms of intoxication in susceptible laboratory animals (guinea-pigs and rabbits), and these infusions are fatal for mice, pigeons, monkeys, and cats, when given subcutaneously. From liquid cultures of the bacillus a poisonous filtrate having similar effects may be obtained, and by adopting the measures usually practised to obtain bacterial poisons a toxin of extraordinary potency can be isolated from the cultures of the organism, the minimum fatal dose being considerably less than that of the tetanus toxin. Physically and chemically this substance has been found to resemble the toxins of diphtheria and tetanus; and, like these, it may be used in producing an artificial immunity in animals by properly graded doses. Protection against the poison as found in contaminated meat or as formed in culture media is eventually attained, and the blood-serum of these immunized animals is antitoxic, the antitoxin being a prophylactic and curative agent against the *botulinus* bacillus and its poisons.

The Organism of Asiatic Cholera.—This much-dreaded malady, having its home in India and occasionally visiting other parts of the torrid and

temperate zones in devastating epidemics, is associated with a micro-organism first thoroughly studied by Koch in 1884, and since generally regarded as the etiologic agent in cholera. It is called *Spirillum cholerae*, *Comma bacillus*,



FIG. 95.—*Spirillum* of Asiatic cholera, from a bouillon culture three weeks old, showing long and degenerate forms. $\times 1000$ (Fränkel and Pfeiffer).

Vibrio cholerae, and is a rather small, slightly curved rod, often grouped so as to make distinct elongated spirils.

Under ordinary conditions of laboratory cultivation and as found in choleraic stools from different individuals, in different epidemics, and in various parts of the world, the morphologic variations presented by Koch's spirillum are insignificant; the only marked ones are the so-called degenerate or involution forms seen after growth for long periods on artificial culture media or in unfavorable surroundings. This morphologic constancy contributes an important element in the diagnosis of cholera, which has often been made by an examination of the suspected dejecta or surfaces soiled by dejecta.

The organism is motile and has terminal flagella; its growth on ordinary media is noncharacteristic; it does not ferment sugars, but has proteolytic power, liquefying gelatin and blood-serum. The ferments, bacteriotrypsin and invertin, are probably uniformly produced in favorable media, while labferment is not so regularly formed. Indol is formed in proteid media in large amount. During the first few hours or days of a new culture, nitrites are also produced, and the indol test may be performed by the addition of sulphuric acid alone, this constituting the well-known "cholera-red reaction" (nitroso-indol reaction). Some of the vibrios closely allied morphologically to the cholera vibrio, and organisms like the bacillus of diphtheria, likewise give this reaction. Physiologic variability has, however, been observed in spirilla obtained from cholera cases, such as difference in the rate of liquefaction of gelatin and blood-serum, absence of the nitroso-indol reaction, and negative pathogenic effects; but such deviations have generally been only temporary, and gradually disappeared under routine laboratory cultivation.

Notwithstanding the freedom with which the organism of cholera adapts itself to laboratory conditions, it seems to be well advanced toward obligate parasitism in the human being. At least, it is certain that all attempts to trace its life history outside of the human body have failed to show that it thrives in the saprophytic habitat imposed by natural conditions. Its longevity varies considerably, but, on the whole, is short, under the stress of external conditions. It has been repeatedly found alive in media like contaminated water and soil, and there is little question that through such means it has found its way from person to person. No evidence exists of its sojourn in an intermediate animal host by which it is propagated and distributed, but, like the organism of typhoid fever, it seems quite reasonable to believe that the agency of insects may be an important factor in favoring distribution, especially to human foodstuffs. But there is abundant proof that in the small intestine of the cholera patient the spirillum of Koch finds con-

ditions well suited to its vegetative existence. Even here, however, unfavorable factors, such as peculiar reactions of the intestinal contents, or that state which we are pleased to style "increased vital resistance," occasionally hamper the organism, particularly in its pathogenic tendencies, in witness of which we have the finding of cholera vibrios in the stools of seemingly healthy individuals in contact with epidemic cholera.

Morbid Effects.—The route by which cholera vibrios gain access to the human organism seems to be by the gastro-intestinal canal exclusively. Experiments on animals tend to show that the acidity of normal gastric juice has a harmful influence; and, in order to obtain positive effects from feeding-experiments, the gastric secretion is neutralized and intestinal peristalsis retarded by medicinal agents. Whether such a condition must precede spontaneous cholera infection in man, and, if so, how it is brought about, are not known.

Once having gained access, the morbid conditions excited by the spirillum manifest themselves primarily in the small intestine by an inflammatory reaction varying in extent and severity. There may be only a hyperemia, or the mucous membrane may be soft and edematous and studded with hemorrhagic ecchymoses. Inflammation with more or less swelling and superficial necrosis of the mucosa may appear, particularly in the lower ileum, and a swelling of the intestinal lymphoid follicles, both solitary and agminated, is a constant phenomenon. In more advanced cases of severe intestinal infection, diphtheric plaques may appear on the mucosa, and the necrosis may advance to the stage of ulceration, with considerable defects in the lining of the bowel. In all stages the intestine is filled either with the thin, rice-water, flocculent material so characteristic as a clinical evidence of the disease when discharged, or with a bloody, offensive fluid. In this fluid the vibrios are present almost unmixed; they also appear in the superficial epithelial cells of the mucosa, sometimes penetrating well into the submucous lining. Exfoliation of the superficial epithelium is quite constant, as a consequence of which these flakes containing spirilla are found in the stools. Of the other gross lesions, those shown in the kidneys are most marked; here well-pronounced parenchymatous degeneration is seen, and in certain cases the damage to the kidney is of high degree, while the intestinal alterations are slight (uremic form of cholera). In the liver, spleen, heart, lungs, and brain, the gross changes are those common to many acute infections, being more or less marked in different cases. However, even where the naked-eye evidences of visceral alterations are not pronounced in cholera, the disease may nevertheless have caused grave alterations; for precise histologic study shows here, as in the case of most other microbic affections, considerable disturbance. Thus it has recently been shown that in fatal cases of Asiatic cholera the hyperemia and punctate hemorrhages of the brain are accompanied by intense degenerative changes in the ganglion-cells—pigmentary atrophy, vacuolation, chromatolysis, and the immigration of leukocytes. The cells of the cerebral capillaries show fatty and granular degeneration also. In the abdominal viscera, degenerative and necrotic changes appear in the parenchyma, and an inflammatory reaction in the stroma. Focal necrosis is not uncommon, especially in the liver, and here the blood-vessels of the interlobular and intralobular tissues may contain thrombi, in some of which cells of the splenic pulp can be recognized, while free liver-cells appear in others. The splenic cells doubtless find their way here by the

portal route; and, while the presence of liver-cells has not been noted in the pulmonary vessels, their presence might be readily expected from the circulatory mechanism.¹ Insular necrosis in the liver of cholera cases sometimes at least may be ascribed to emboli of splenic cells. The formation of such emboli is probably the result of a toxemia, but the exact mechanism of the phenomenon is not known. In the case of cholera, however, such an intoxication or embolism must be held to account for lesions in parts of the body remote from the gastro-intestinal canal, since the spirilla are generally absent from the blood and organs in fatal cases.

Cholera Toxin; Immunity; Protective Vaccination.—That the fatal results of infection by the cholera vibrio were due to an intoxication was held by Koch in his early studies of the disease. From our present knowledge it appears that, like the typhoid bacillus, the organism of cholera elaborates both a soluble diffusible toxic substance and one intimately bound with the protoplasm of the bacterial cell. This latter poison, studied with especial care by Pfeiffer, is obtained by killing actively growing vibrios. Guinea-pigs, after intraperitoneal inoculation, react very promptly and with symptoms of collapse, such as are observed in the algid stage of cholera in man. With smaller doses a temporary intoxication and fall of temperature occur; and, after complete recovery (ten to fourteen days), living, virulent vibrios from recent cultures may be cautiously introduced in gradually increasing quantities at appropriate intervals until the usual reaction ceases. By this procedure an immunity is conferred, and the blood-serum of the immunized guinea-pig possesses several remarkable properties. Thus it produces rapid cessation of motility and clumping of living cholera vibrios (*agglutination reaction*), followed by a disintegration and solution of the bacterial cells (*bacteriolysis*) when mixed in proper proportions with the suspended organisms outside of the living body. This interesting phenomenon, first noted by Pfeiffer and more fully investigated by Gruber and Durham, prepared the way for the agglutination reaction as now applied to the diagnosis of several infectious diseases, especially typhoid fever, and for the opening of the new field of cellular reaction and cellular solution which is being extensively investigated at present. It was also found that a similar inhibiting and destructive effect could be produced by injecting the serum and living vibrios into the peritoneal sacs of living guinea-pigs. Furthermore, the blood-serum of human beings who have recently recovered from an attack of cholera also possesses these agglutinative and bacteriolytic properties. In bacteriologic diagnosis these observations found practical application, since the serum of naturally or artificially immunized animals exerted its specific effect only on the typical members of the cholera-spirillum group, but not on several cholera-like vibrios hitherto believed to be related to it or identical with it. For practical application in treating cholera in human beings, these experiments have thus far been unavailing, and the method of pro-

¹ Cellular emboli, composed of elements from the splenic pulp, bone-marrow, endothelioid cells originating in lymph-nodes, and even liver-cells, have lately been recognized in the course of careful histologic examinations as occurring in a number of acute infectious diseases—for example, diphtheria, scarlet fever, pneumonia, typhoid fever, gas bacillus infection—and also in eclampsia. The significance of this process is not yet clear; in some cases it must be looked upon as an occurrence of the death agony, at other times all appearances point to the formation of cellular emboli during life, when they may be an important factor in determining lesions of the viscera in which they lodge. Focal necrosis may thus be induced by these emboli when lodging in arterioles or capillaries, the necrotic focus being really a microscopic infarct.

tective vaccination introduced by Haffkine, consisting in the injection of attenuated cholera cultures in two doses of increasing strength, must still be regarded as an experimental stage, though not without hopeful prospects.

Besides the spirillum of Koch, a series of vibrios with similar morphologic, physiologic, and pathogenic properties have been described, among which it will be sufficient merely to mention the vibrio of Finkler and Prior, the *Vibrio tyrogenes* of Deneke, the *Vibrio Metschnikovii* of Gamaleia, and a series of cholera-like vibrios or water vibrios obtained from water-supplies by bacteriologists in various parts of the world. Notwithstanding their manifest affinities with the cholera spirillum, there is little disposition at the present time to displace the vibrio of Koch from its etiologic position.

The Spirillum of Relapsing Fever.—The spirochete of recurrent fever, first described by Obermeier, an assistant of Virchow's, in 1873, is placed among bacteria by general consent, although this disposition of the organism is founded on very limited knowledge, as nothing whatever is known of its history outside of the body of an infected animal, nor of its stages within the host. It is not impossible that the suspicion of Saccharoff concerning the protozoan (hematozoan) nature of this parasite is correct, and that the peculiar flexible and highly motile spirilla observed in the blood of relapsing-fever patients during the febrile paroxysm are only one stage in the life history of the organism. Possibly the round, refractive bodies seen especially in the spleen when the fever subsides, and the intracellular whorls of living spirilla in the splenic pulp, described by Metschnikoff, are further steps in the development of a sporozoan parasite. This much may be said, that all attempts to secure and cultivate this spirochete by bacteriologic devices have failed, and it is concluded that the organism either represents a bacterium that has reached an extraordinary degree of obligate parasitism, or that the spirilla represent a stage in the development of a protozoan organism which, like some others of its kind, does not admit of artificial cultivation by ordinary methods. Nothing is positively known concerning the mode by which recurrent fever is transmitted from person to person. Klebs some years ago suggested, from analogy with occasional cases of anthrax, that insects might be found to serve as vehicles; and this view has lately been revived, put to the experimental test, and strengthened by infecting monkeys with recurrent fever through the agency of bedbugs. The infection has also been transmitted to the human fetus *in utero*.

Obermeier's spirillum appears in the blood of relapsing-fever patients just before and during the attack of fever, subsiding in the interval. By means of the infected blood the disease has been inoculated from man to man, and man to monkeys. In the latter animal the spirillum has been found in the spleen, bone-marrow, lymph-glands, liver, and kidneys. Con-

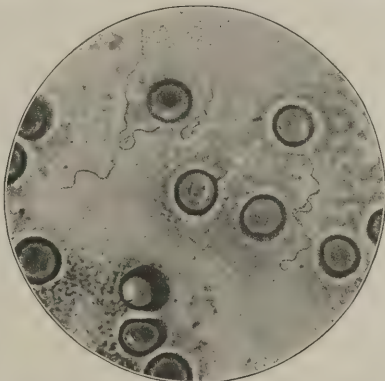


FIG. 96.—Spirillum of relapsing fever (Karg and Schmorl).

trary to Metschnikoff's assertions, splenectomy appears to have no marked influence on the progress of the infection. Phagocytosis, especially by leukocytes, is in active progress during the afebrile period, and the evidences of disintegration, which many spirilla show, result no doubt from the action of a bactericidal substance in the blood-serum, the nature of which has not been determined. But in the case of the spirochete septicemia in geese, which closely simulates relapsing fever in man, Gabritchewsky claims to have produced an immunizing and curative serum in the horse by intravenous injections of infected goose's serum.

The gross lesions of fatal relapsing fever are noncharacteristic, the swollen spleen and occasional parenchymatous nephritis being most marked. Careful histologic studies of the infected organs have not been reported. The blood during life may contain free melanin granules, and similar hematogenous pigment appears in the leukocytes during the afebrile period.

The Pyogenic Staphylococci.—Among the pathogenic spheric bacteria (*Micrococci*), those arranging themselves in grape-like clusters through division in various planes, and designated *Staphylococci*, are the best known. For the last twenty years, micro-organisms of this kind have been recognized as bearing some relation to suppurative lesions in man and other animals; and since the precise investigations by Ogston in 1881, and Rosenbach, Krause, Passet, and others in 1883-84, both the staphylococci and the chain-forming micrococci (*Streptococci*) have been regarded as the exciting agents of these pathologic processes.

The pus-producing staphylococci constitute a bacterial group the morphology of which is quite constant, but the members of which differ in certain minor physiologic characteristics, such as pigment-production or the capacity of peptonizing proteid culture media; they also vary as to their pathogenic effects in the human subject or in experimental animals. It will be convenient, however, to consider them under one head, particularly so far as their morbid effects are concerned, since it is a well-determined fact that any one of the races may show extreme virulence or be relatively innocuous. The chief member of this group, and the one most commonly met, is *Staphylococcus pyogenes aureus*, characterized by the golden color of the pigment formed in favorable media and by its virulence. It liquefies gelatin and coagulates milk with resulting acidity. *Staphylococcus pyogenes albus* is closely related to the foregoing, being also a peptonizing organism and coagulating milk, but it is devoid of the power of elaborating pigment like the aureus. Between these two is the lemon-yellow pus staphylococcus (*S. pyogenes citreus*), with its lighter yellow pigment. Then there is a series of nonliquefying staphylococci, represented by *S. cereus albus*, nonpigmented, and *S. cereus flavus*, producing yellow pigment. That several of these cocci, if not all, are but variations of a common stock seems a most reasonable view, although definite scientific proof has not yet been obtained.

These micrococci can exist in saprophytic surroundings, as shown by their presence in water, air, and dust, although as inhabitants of air and dust they have been recovered chiefly from situations like hospital wards, surgical operating-rooms, morgues, etc., where their occurrence may be accounted for readily. They are common in man and the mammals, one nonpigmented variety closely allied to *S. pyogenes albus* being a constant inhabitant of the skin (*S. epidermidis albus*), while other varieties, like *S. pyogenes aureus*, also

abound on the cutaneous surfaces, in the ducts of sweat-glands and sebaceous glands, and about hair-follicles. In the mouth, and more rarely in the nose, auditory canal, or conjunctiva, one or another of these staphylococci is found. As organisms of latent parasitism, the pyogenic staphylococci are also of importance, lying dormant, especially in the superficial lymph-glands, the tonsils, and at times also in the scars of healed infected wounds, in bone lesions, and in the viscera. To this latent microbial parasitism of the lymph-glands, at least, it seems quite reasonable to ascribe some of the peculiar cases of *cryptogenetic infection* in which no demonstrable orifice of invasion is discovered—a form of infection in which the pyogenic micrococci sometimes participate.

Morbid Effects; Toxic Products; Immunity.—As their name indicates, the principal races of the staphylococcus group are pre-eminently organisms of suppuration. In the skin their harmful effects are manifested by such lesions as pustular acne, furuncles, and carbuncles; they are also by far the most frequent agents of inflammation and suppuration in traumatic infective diseases. In inflammation and suppuration of the mucous membranes throughout the body, the pus staphylococci are prominent, either alone or in association with other pathogenic micro-organisms. The same holds true of inflammations of serous membranes. In like manner any of the viscera may be attacked, generally as a secondary invasion from some external local affection. Acute bone affections, such as periostitis and osteomyelitis, are commonly ascribed to these cocci. Multiple synovitis, at first simulating acute articular rheumatism so closely as to be indistinguishable clinically, and followed by acute ulcerative endocarditis and septicemia or pyemia with no apparent local primary affection (“cryptogenetic” staphylococcus infection), is one of the several complicated morbid processes induced by these organisms.

From the preceding rehearsal it is evident that the staphylococcus group may participate both in local and general diseases. From a local lesion like an infected wound, osteomyelitis, or phlegmon, infection may traverse the lymph-channels (lymphangitis) to reach the regional lymph-glands (lymphadenitis), and, while generally stopped by these barriers, it may proceed either by the lymph-vascular or blood-vascular route to more remote parts. Invasion of the systemic blood-stream taking the form of a bacterial septicemia (bacteremia) is a possible consequence, or the cocci may set up suppurative foci in various remote tissues or viscera, producing the condition known as pyemia. In certain parts of the body, particularly from the phlegmons about the nose, retrograde infective thrombosis of adjacent veins may be produced, the thrombi reaching the cranial sinuses and setting up inflammatory or suppurative changes in the meninges, or entering the general venous blood-stream to be taken to the heart, whence the bacteria may be conveyed to the body at large. Again, from the local seat of infection the staphylococci are carried to the heart, here to establish vegetative endocarditis, fragments of the infective vegetations being swept away as emboli to reach certain viscera, where infarction is quickly followed by inflammation and often abscess.

Suppuration as induced by the pyogenic micro-organisms, and particularly by the pyogenic cocci, is a reaction to chemical irritation in which the wandering polynuclear leukocytes take the chief part. Some substance elaborated by the micro-organism and seemingly a part of its protein is of a toxic nature, with the peculiar property of attracting wandering cells when

introduced into animal tissues (positive chemotaxis); these cells, migrating chiefly through the blood-vessels, accumulate in the affected region, accompanied by such vascular phenomena as hyperemia and stasis. A reaction of the fixed-tissue cells is also induced, proliferation resulting. As a further effect of the toxins, the accumulated cellular elements, both migratory and fixed, soon undergo degenerative changes, either albuminous or fatty in nature, and the living and dead cells, cellular detritus, and the liquid substratum make the principal constituents of pus. Sometimes the necrotic phenomena are much more in evidence, gangrene of surrounding tissues with extensive sloughs being caused. In the purulent exudate, the cocci are found both free and inclosed in the protoplasm of the cellular constituents. In many cases this taking-up of the bacteria by the fixed and wandering cells is a protective process (phagocytosis), in which the micro-organisms are inhibited in activity or killed. At other times the polynuclear leukocytes, lymphoid cells, and plasma-cells suffer destruction, and to other cells, especially the large endothelioid phagocytes, falls the labor of removing the detritus. In mild or more chronic suppurative affections and in those undergoing reparative changes, lymphoid cells and plasma-cells—and later mast-cells—make their appearance.

Susceptibility to pyogenic infection is subject to considerable variation, some individuals being easily and repeatedly infected, others enjoying a high grade of active immunity. Many factors, such as previous infections and debility from other diseases, increase the individual predisposition. Many of the influences which arouse latent and apparently healed pyogenic foci into activity are unknown; but cold, traumatism, and incidental diseases are certainly fruitful causes. Of similar nature to the latent foci are the smouldering lesions from which toxic products or attenuated micro-organisms are periodically transported.¹

Experimental inoculation with the staphylococcus group varies considerably in its results. Generally the reaction to subcutaneous injections is a mild and transient inflammation or a localized abscess. Fatal purulent peritonitis is usually caused by sufficiently large intra-abdominal doses, and intravenous injections quite uniformly produce metastatic abscesses in the viscera, and death with general bacterial septicemia. Ulcerative endocarditis may be produced by fragments of potato cultures introduced in the veins or by mechanically injuring the heart-valves before or immediately following intravenous injection of staphylococci, and traumatism or fracture of bones in animals the blood of which contains the cocci is followed by osteomyelitis. Dead pus cocci also excite local leukocytosis and pyogenic reaction.

The peculiar poison upon which the activity of these micro-organisms doubtless depends has not been isolated, but artificial immunity has been induced in animals by injections of the living or dead cocci, and the blood-serum of these subjects appears to have some protective and antitoxic property.

An ordinary external saprophytic coccus, also found as a lodger in the healthy nose, mouth, and throat, which occasionally plays a parasitic and

¹ In this connection, too, it may be well to recall the view lately advanced, that the osseous and nervous lesions (hydrocephalus) of *rachitis* are the result of a chronic infection with attenuated pus cocci or a chronic intoxication with their products; and possibly the lymphoid hyperplasia producing the anatomic picture of the *lymphatic constitution*, as frequently seen in rickets, is a response to the same irritant.

pathogenic role in man, is *Micrococcus tetragenus*, described by Koch and Gaffky, so called because of its prevailing tendency to appear in groups of four elements, comparable to two diplococci side by side. As found in secretions and tissues, it shows a well-defined capsule. It develops readily on ordinary culture media as a nonliquefying, nonchromogenic growth, both in the brood-oven and at room-temperature. Milk is not coagulated, nor are the sugars fermented. Its culture on agar, blood-serum, and potato somewhat resembles that of the pneumobacillus, a resemblance heightened by a "nail" formation in gelatin stabs.

As a pathogenic micro-organism it has been found in localized suppurations, such as abscesses about the teeth, nose, mouth, neck, and axilla, in bronchitis, pleuritis, pericarditis, peritonitis, and even meningitis. Several cases of septicemia ascribed to it have been recorded. It has been noted also in pseudomembranous angina with severe constitutional disturbance. When administered in sufficiently large doses it proves pathogenic for guinea-pigs and rabbits, producing localized abscesses and general hematic infection. White mice are more uniformly susceptible to small doses.

The Pyogenic Streptococci.—The chain cocci of pus are most frequently encountered in their parasitic abode, and while evidently capable of existing, for a time at least, outside of the animal body, such phenomena as their comparatively slow growth on culture media and the short-lived existence of many of the races point to a well-advanced adaptation to parasitism. These characteristics are not uniform, however, and the various pathogenic pus-producing streptococci broadly comprehended under the name *Streptococcus pyogenes* are therefore to be looked upon as a bacterial group of several closely related races or varieties.

Some of the more common variations in form to which these streptococci are subject appear in the length and arrangement of the cocci composing the chains when growing in fluid media, there being cultures in which diplococci alone appear, others with chains of four to six small cocci, and longer chains with both small and larger elements; hence such names as *S. longus*, *brevis*, *conglomeratus*, *gracilis*, and *involutus* have been applied, some observers implying thereby a specific difference, but certainly on insufficient grounds, since it has been found that comparatively slight changes in culture media or a sojourn in the animal organism is effective in changing these morphologic characters. The linear continuity by which the streptococcus chain is produced results from the division of the individual spheres through an axis uniformly at right angles with the chain. But the plane of division is readily disturbed, the consequence being various irregularities in the chain; among other deviations, a division at an acute angle suffices to start a new lateral chain of cocci looking like a branching from the parent series. Various inhibiting or accelerating influences encountered under laboratory conditions further affect the individual cocci, by which is produced the variation in size so often seen; and some similar influence must be concerned in the production of the occasional bizarre streptococcoid elements which assume the shape and general appearance of polymorphous bacilli, like those commonly shown by the organism of diphtheria. By transplantations from blood-serum to broth it was found possible repeatedly to transform the irregular, bacilli-like elements of a certain streptococcus into minute, uniform, split spherules cohering in extremely long chains.

One of the physiologic attributes of this group of micrococci is relatively

constant, viz., the absence of the peptonizing function—they do not liquefy gelatin; but the rate of growth on artificial media differs considerably in streptococci from different sources. Some cloud bouillon uniformly, others aggregate into globules or flakes and settle along the sides or bottom of the tube, leaving the fluid clear; but these differences are unstable, since one and the same stock may be induced to produce both effects in broth. Milk may or may not be coagulated, and some members of the group show a capacity for producing, in artificial cultures, pigment of a yellowish or reddish tinge.

The pathogenic properties of various streptococci, when tested in white mice and white rabbits, are subject to variation not only in different races, but also in the same race according to the mode by which it is handled. By growing nonvirulent or slightly virulent streptococci in certain media, like bouillon-serum mixture, and transferring from mice to rabbits, it has been found possible greatly to accentuate the pathogenic power of a given culture.

Morbid Effects; Toxins; Antitoxin.—Streptococci of the pyogenes group have been found in a diversity of human maladies, often unaccompanied by other bacterial species. As the name of the type species indicates, they are pus-producing, and they may be associated with all the stages of pyogenic infection, from local inflammation to general septicemia. As excitants of local inflammatory and suppurative phenomena, they are encountered in all mucous and serous membranes of the body, in bones, and in abscesses of such organs as the liver and brain. Among the more common affections in which streptococci are concerned, either alone or combined with other organisms, spreading phlegmon and cellulitis, anginas, lobular pneumonia, synovitis and osteomyelitis, lymphangitis, pleuritis and peritonitis, and puerperal septicemia may be mentioned. Besides this, the chain cocci are constantly found in erysipelas, as originally shown by Fehleisen. It was formerly thought that the streptococcus found by Fehleisen in erysipelas was specifically different from those concerned in the other inflammatory suppurative or septicemic conditions, whence arose the distinctions *Streptococcus erysipelatis* and *Streptococcus pyogenes*. However, it has been satisfactorily demonstrated that the streptococcus of erysipelas may become pyogenic, and *vice versa*. The conditions which they induce depend upon the route by which they gain access to the body, and especially upon their virulence, which, as has already been indicated, may be exalted to an extraordinary degree by certain conditions of cultivation and passage through animals. In short, it has been shown that the activity of a streptococcus which only causes abscess may be exalted to a virulence by which erysipelas, purulent infiltration, or fatal septicemia results. These experiments serve to sustain the views as to the common ancestry and close relationship of the various streptococci, as already indicated by morphologic and physiologic considerations, and to emphasize the desirability of considering them as a single group.

Besides their more active manifestations, streptococci may lie latent, as mentioned in connection with staphylococci.

The morbid histology of general streptococcus lesions is quite similar to that seen after infection by the other pyogenic cocci; hyperemia, blood stasis, emigration of leukocytes, and transudation of serum mark the inflammatory reaction. Various local necrotic effects are seen in the virulent infections, although the tendency to transudation and swelling is more marked than the necrotic and liquefying action in local staphylococcus disease. From the absorption of toxins, or in virtue of the diffusion of the cocci, thrombosis,

embolism, infarction, and focal necrosis occur. In erysipelas the organisms generally invade the lymph-channels, spreading rapidly through them, and at times packing them full. Necrotic alterations appear in the surrounding tissue-cells, and wandering cells are attracted, leading to a dense cellular infiltration, in the midst of which the cocci appear, either between the cells or inclosed in those of phagocytic power. The epithelium of the surface may soften and be raised by transuded fluid, producing vesicles. As a rule, the invasion of outlying areas is first effected by the streptococci, which precede the accumulated leukocytes in their march.

The effects of spontaneous streptococcus infection may be reproduced experimentally both by means of the living organisms and by means of the toxins which the streptococci elaborate in fluid cultures. But these poisons have not been isolated, and they are known only by their effects, which are more or less virulent according to the activity of the stock culture, which, as we have already indicated, may be enormously increased by artificial means. Various animals, when subjected to injections of streptococci of increasing virulence or of toxins of increasing strength, attain an immunity manifested by their resistance to large doses of the most virulent cocci or their poisons and by the presence of an antitoxic substance in their blood-serum. Such a streptococcus antitoxin is manufactured and offered as a therapeutic agent for spontaneous streptococcus infections in man, but the practical results have been far from brilliant. The same may be said of the value of streptococcus toxins and antitoxins for the treatment of inoperable malignant tumors.

Micrococcus Lanceolatus and Meningococcus.—The *Micrococcus* or *Diplococcus lanceolatus* must be looked upon as the specific causative agent of genuine lobar or croupous pneumonia; it has been known under various names since 1880–81, when it was discovered in human saliva by Sternberg, and independently by Pasteur.¹ It often appears in short chains of four to six members or even in longer series. Aside from occasional chain formation, there are other characteristics of the lanceolate diplococcus that show it to be a close relative of the *Streptococcus pyogenes*, and those who have worked most extensively on the question of its variation as encountered under natural conditions and laboratory modifications incline to the view that it is only a variety of the *Streptococcus pyogenes* group. If this is true, it must be regarded as a more highly developed variety in parasitic adaptation, since it has not been found under external saprophytic surroundings and is unusually short-lived under the most favorable laboratory conditions. Like other pathogenic micrococci, it is a lodger or inhabitant of the secretions of healthy human beings; but it is more especially confined to the mucous membranes and secretions of the upper air-passages, abounding in the saliva, in the throat, nose, tonsils, or accessory nasal sinuses, although apparently not flourishing on external surfaces like the skin.

Considered as a species, *Micrococcus lanceolatus* owes its morphologic distinction to the triangular or lance-shaped form of the individual elements of the coccus, whence the name “lanceolatus.” A capsule, appearing about the diplococci when present in sputum or in the blood, is also characteristic. But these morphologic features are inconstant and are liable to variation, especially under conditions of artificial cultivation. Physiologically the

¹ Other names are *Pneumococcus*, *Microbe septicémique du salive* (Pasteur), *Micrococcus Pasteuri* (Sternberg), *Pneumonimikrokokkus* (Fränkel), *Diplococcus pneumoniae* (Weichselbaum), *Streptococcus lanceolatus*, etc.

behavior, as exhibited in its growth on agar, gelatin, potato, in broth, and in milk, is similar to that of the chain coccus of pus, only that it is somewhat more susceptible to change in temperature and is of briefer longevity. Its pathogenic properties, as tested upon rabbits and mice, is more uniform than that of the various races of streptococci, a fatal septicemia being generally produced by relatively small doses injected subcutaneously or intravenously. Injections into the peritoneal cavity produce peritonitis and septicemia; those in the lung or trachea, pneumonia; in the meninges, meningitis; in the joints, synovitis; and small subcutaneous injections cause local abscesses.

Morbid Effects; Immunity.—As shown by Fränkel and substantiated by the exhaustive studies of Weichselbaum in 1886, this coccus is the particular parasite of lobar pneumonia. In all probability this formidable disease must, in certain cases at least, be looked upon as an *auto-infection* by micrococci constantly inhabiting the upper air-passages in health; and while we do not know precisely what conditions conspire to increase the virulence of the micro-organism or to lower the resistance of the host, something of this kind must happen to enable the parasite to pass the barrier afforded by the healthy ciliated epithelium of the upper air-tubes and to overcome the resistance of phagocytic cells. Undoubtedly such local disturbances as angina, tonsillitis, rhinitis, and the like, play a part in opening the way for the further advance of the infection, and at times it seems that the organism of pneumonia has already entered the blood-stream from some local portal of invasion, like the tonsils, before the morbid process in the lungs has made headway. As a result of the irritation of this infection in the lungs, a cellular exudate appears in the pulmonary alveoli, composed at first of cells with single nuclei larger than ordinary leukocytes, mixed with red blood-cells. Polymorphous leukocytes are not present in the earlier stages of lobar pneumonia. Lymphocytes and later plasma-cells make their appearance in the alveoli and the interstitial tissues. Leukocytes with polymorphous nuclei abound in the affected tissues by the third day, and from this period large mononuclear endothelioid phagocytic cells, with inclusions composed principally of red blood-cells, pigment, and polynuclear leukocytes, are to be found. Fibrin is deposited, at first about the periphery of the alveoli. Thrombi appear in the blood-vessels, especially the capillaries, and in the stage of gray hepatization fibrinous thrombosis may attain a widespread extent in the affected tissue. Some of the blood-vessels also contain emboli of giant cells from the bone-marrow, and in certain cases parenchymatous emboli are quite numerous. As resolution advances, plasma-cells become more abundant and mast-cells not infrequently make their appearance. That the epithelium of the pulmonary alveoli suffers damage is evident from the number of exfoliated cells appearing in the pneumonic exudate. The source of the cells first appearing in the exudate is not clear; they probably arise by proliferation from the lining cells of the alveoli. Similar cells appear in the early stages of the pleural exudation which so commonly accompanies lobar pneumonia, and here lymphoid cells, polynuclear leukocytes, large phagocytes, fibrin, and plasma-cells are found as the process advances. Excessive localization of leukocytes and transudation of serum lead to empyema, which not rarely follows lobar pneumonia.

But while lobar pneumonia is the chief affection to be ascribed to the lanceolate micrococcus, it is by no means the only pathologic process in

which this organism participates. Complications of lobar pneumonia, like pleuritis, pericarditis, endocarditis, peritonitis, and meningitis, are also due to its pathogenic effect, either alone or in company with one of the commoner pyogenic cocci. A general blood-invasion, with wide dissemination of the diplococcus (diplococemia), is also possible, and sometimes the pneumonia seems to be but one of the local expressions of such an infection. On these occasions the general visceral changes peculiar to acute infectious diseases are found, and these parenchymatous changes, affecting principally the lymph-glands, spleen, kidneys, and liver, are present in whole or in part in fatal pneumonia where the inflammatory process remains confined to the lungs. Bronchopneumonia is sometimes produced by this coccus, and it also takes part in such diseases as synovitis, periostitis and osteomyelitis, adenitis, parotitis, mediastinitis, pericarditis, endocarditis, appendicitis, peritonitis, otitis, and meningitis, in which no primary pulmonary affection has occurred. It is very significant that, in many of these diseases, angina, rhinitis, or tonsillitis precedes the more distant affections. Phlegmonous affections and abscesses sometimes contain *M. lanceolatus* in pure culture.

In human beings who have recovered from pneumonia, a protective and curative substance is said to be present in the blood-serum; but satisfactory experimental proof of this statement is lacking, and there certainly is little ground as yet for the use of this serum for therapeutic purposes in man. Immunity in the highly susceptible rabbit may be secured by intravenous injections of small amounts of a potent culture or by the use of filtered cultures or cultures heated to 60° C., but the serum in these cases is of questionable protective value. More recent experiments in rabbits, goats, and horses with cultures of highly developed virulence seem more promising, for the serum of the immunized animals gives experimental evidence of possessing protective and curative virtues; but as for use in actual human therapy, there is little at the present time to indicate the value of such an agent. It has been found, however, that the serum of human beings suffering from pneumococcus infection, or of animals artificially infected, causes agglutination of these micro-organisms.

Apparently even more highly adapted to a parasitic existence than the organism we have just considered is the meningococcus (*Diplococcus intracellularis meningitidis* of Weichselbaum), which is found principally in the substance of polymorphonuclear leukocytes from one or another of the several lesions with which it is associated. Both its biscuit shape and its intracellular abode liken it to the gonococcus. Subjected to the usual conditions of laboratory cultivation, this organism thrives but poorly; it rarely grows on any medium except coagulated blood-serum, and here only scantily, quickly dying in the original culture or when transferred to glycerin-agar or broth. There is nothing characteristic about the cultures except their feeble vitality, and nothing is known about variations in morphology or physiology. Contrary to the rule for the pyogenic staphylococci, streptococci, and *Micrococcus lanceolatus*, the meningococcus does not retain the stain when treated after the Gram or Weigert method.

The diplococcus intracellularis is considered by many observers the specific etiologic agent of epidemic cerebrospinal meningitis. Certainly the majority of cases of acute meningitis, endemic or epidemic, have either the lanceolate micrococcus or the meningococcus associated with them, and it seems proper to charge this affection chiefly to them. Both organisms have their abode in

the nose; through the ready route afforded by the accessory nasal sinuses, infection of the meninges is easily produced, especially when the resistance of the mucous linings of the nose and sinuses is lowered by catarrhal affections. It is not impossible that in this way the diplococci or some other pyogenic cocci gain access to the meninges, brain, and spinal cord, exciting not only the acute purulent form of meningitis, but also the more chronic forms, like meningo-encephalitis, the consequences of which are seen in infantile paralysis, idiocy, etc.

Besides being found in acute meningitis, the meningococcus has been discovered also in the pneumonic lung, in synovitis, in abscess of the myocardium, in multiple arthritis complicating meningitis, and in tonsillar abscess and pseudomembranous conjunctivitis associated with meningitis. It has been demonstrated in the circulating blood during life, thus showing that it may cause a condition of general septicemia; and a valuable diagnostic procedure is its discovery within the polynuclear leukocytes of the meningeal fluid obtained by lumbar puncture. Not uncommonly it is mixed with other pathogenic organisms, especially the pathogenic cocci. In experimental animals, subcutaneous inoculations of pure cultures of the meningococcus are not fatal; but, when introduced into the peritoneum or pleural cavity, fibrinopurulent inflammation results, usually ending fatally. Cerebrospinal meningitis has been produced in the goat by subdural inoculation of a broth suspension of the organism.

Histologically the meningitis provoked by this organism resembles ordinary suppurative leptomeningitis. The meningeal exudate consists principally of polynuclear leukocytes, of large endothelioid cells, and some fibrin. Lymphocytes appear in the perivascular sheaths of the blood-vessels.

Gonococcus.—The biscuit-shaped diplococcus discovered by Neisser in 1879, and styled *Micrococcus* (*Diplococcus*) *gonorrhoeae*, or simply gonococcus, is the specific etiologic factor in gonorrhea. Morphologically it most closely resembles the meningococcus, agreeing also in its refusal to retain the stain after the procedure of Gram. Nothing is known of its capacity to exist under saprophytic surroundings, all evidences pointing to its advanced adaptation not only to a state bordering on obligate parasitism, but also one apparently necessitating the choice of the human body as a habitat, for it has never been found as a parasite in other animals. For a long time, failure attended all efforts to cultivate it artificially; but with improved media, especially those containing proteids from the human subject, as obtained by mixing ascitic or hydrocele fluid or human blood-serum with agar, cultures have been obtained. The further addition of human urine appears to improve the serum-agar. On these special culture soils a growth of the gonococcus is obtained by smearing the secretions, such as urethral pus, over the surface and placing the cultures in the thermostat. For ordinary clinical demonstration, however, the discovery of the characteristic biscuit-shaped diplococci or tetrads in the suspected secretion, particularly when lying in heaps in the protoplasm of polynuclear leukocytes, and their failure to stain by Gram's method, generally suffice for diagnostic purposes.

Morbid Effects.—Contrary to the ideas originally held, the gonococcus is not confined to the urethral lesions and discharges of gonorrhea. This fact has been strikingly brought out since the introduction of successful culture methods, and we now know that it is associated with a variety of local conditions that may complicate gonorrhea. In ophthalmia neonatorum its

presence has also long been known. But it has remained for comparatively recent investigations to establish its association with arthritis, tendosynovitis and perichondritis, salpingitis and localized peritonitis, acute and chronic cystitis and pyonephrosis, adenitis, pleuritis, myocarditis, and ulcerative endocarditis. That the gonococcus may even produce a general blood-infection seems proved. There is no doubt concerning the pronounced pyogenic activity of this coccus. It produces both local inflammatory and suppurative reactions in the mucous membrane of the genito-urinary tract and of the eyes, and induces the various metastatic purulent or seropurulent processes which have been enumerated.

Experimental inoculations have not yielded brilliant results, doubtless on account of the unsuitability of the lower animals as hosts; but local inflammation and suppuration follow the introduction of living gonococci on sterile foreign substances, and dead cultures provoke a nonpurulent peritonitis. Typical gonorrhea has been produced in man by inoculations of pure gonococcus cultures into the urethra, but the mucous membranes of animals seem entirely refractory to inoculations both with cultures and with gonorrheal pus. The toxic substances to which the gonococcus owes its pathogenic activity are not well known. They appear to reside in the bacterial cell, since the dead organisms are capable of causing the usual inflammatory reaction. It has been found possible to render experimental animals refractory to gonococcus inoculation by the use of graduated doses of the living or dead organisms, but no success has thus far attended the efforts to obtain a preventive, protective, or curative serum from gonococcus-immune animals.

PATHOGENIC BUDDING AND FILAMENTOUS FUNGI.¹

Introduction.—Long before the bacteria were considered as pathogenic agents, certain organisms belonging to the higher Thallophyta (algæ and fungi) of the great subdivision of Cryptogamia (flowerless plants) were recognized as factors in human diseases. In 1837 the parasite of favus was seen by Remak; again noted by Schönlein in 1839; and, together with the fungi concerned in thrush and herpes tonsurans, accurately described by Gruber in 1841–1844. Since these early descriptions a large number of thallophytes have been found upon or within the human body, sometimes existing as messmates or passenger parasites, again as harmful, disease-provoking invaders. Within the last few years new species have been discovered, some of them concerned in grave morbid processes, so that the study of the pathogenic nonbacterial fungi has become an important branch of pathology (pathologic mycology). Not all the fungi belonging to the nonbacterial Thallophyta are parasitic, of course; a considerable number of

¹ In the discussion of this topic, free use has been made of Blanchard's section, "Parasites Végétaux à l'Exclusion des Bactéries," in the *Traité de Pathologie Générale* of Bouchard, tome ii., and his classification of these pathogenic organisms has been adopted in most part. For a more exhaustive treatise, the student is referred to this article. Good reviews with bibliographies will be found in Eppinger's *Die durch Cladothrichsen (Streptothrichsen, etc.) hervorgerufenen Erkrankungen*, and Ricker's *Spross- und Schimmelpilze beim Menschen*, in *Ergebnisse der allgemeinen Pathologie und pathologischen Anatomie des Menschen und der Tiere* of Lubarsch and Ostertag, Erste Abteilung, and in Busse's *Ueber pathogenen Hefen und Schimmelpilze*, *ibid.*, Fünfter Jahrgang, 1898. A detailed consideration of pathogenic yeast fungi is presented in Busse's monograph, *Die Hefen als Krankheitserreger*, Berlin, 1897. An older but still valuable work is Baillon's *Traité de botanique médicale cryptogamique*, Paris, 1889. The current journals on Parasitology and Pathology should also be consulted.

groups, such as the algæ, slime-moulds, seaweeds, contain chlorophyll and are independent aquatic plants (marine or fresh-water), while many others pass an exclusively saprophytic existence. But it is particularly among chlorophyllless thallophytes that a large group of parasitic vegetable organisms is found, many infesting various kinds of higher plants, low and high orders of animals, and finally man. Among the fungi parasitic upon plants, one has but to recall the blights, rusts, smuts, moulds, and mildews, which sometimes do great damage to fruits and vegetables. They also infest lower animals, notably insects, which often succumb to their ravages, a familiar example being the fly fungus (*Entomophthora muscæ*).

In botanic position the fungal thallophytes stand lowest in the scale of cryptogams, coming in relation with the asexual, unicellular schizomycetes. This contact with the bacteria is so close as to render distinction a matter of difficulty, especially in the case of the more minute fungi, and our knowledge is still too indefinite to make distinctions final. The same considerations apply to the matter of classification of these fungi, which has already undergone several revisions and is still far from perfect. As a rule, however, these organisms are larger and therefore more readily studied than bacteria, and many of them exhibit characteristic sexual processes. But as in the bacteria, the morphologic variation to which these fungi are subject often becomes confusing, and it is through the different interpretations placed upon these variations that disagreement among systematic mycologists has arisen. As a case in point, it may be remarked that some authorities deny the existence of yeast fungi (blastomycetes or budding fungi) as an independent order, claiming that the usual oval yeast-cells are only conidia or nonsexual spores of filamentous fungi.

The *morphology* of the higher parasitic fungi is more complex than that of bacteria. The characteristic structure of the organisms is the vegetative body or thallus, generally a mass of filaments or threads, termed *mycelium*, the single threads of which are *hyphæ*. The thallus takes the place of the root, stem, branches, leaves, and flowers of the Phanerogamia, and, instead of producing seeds to further the reproduction of the fungi, round or oval bodies called *spores* are formed. The spores multiply by a process of budding or gemmation, which in certain species, like the yeasts, becomes widely diffused. Under proper vegetative conditions the spore gives rise, by a process of germination, to a mycelial filament which ramifies more or less extensively, and generally remains unicellular in spite of the considerable size it sometimes attains. The continuity of the mycelial hyphæ is not broken by a regular process of division, but by the formation of walls or *septa* at irregular intervals. The vegetative stage terminates by the formation of organs of fructification which produce the spores, these organs appearing on special hyphæ distinguished from the remainder of the mycelium by the limitation of their growth and their special structure. The formation of the spores upon these hyphæ takes various types, of which five may be distinguished, thus :

The *Exospores* or *conidia* (nonsexual spores) arise on the extremity of the germinal hyphæ by a process of budding or septation. The resulting spores are usually arranged in a linear series. In some cases a difference is manifested in the spores: larger ones, *macroconidia*, and smaller ones, *microconidia*, being carried by the germinal hyphæ or *sporophores*, which may be similar or dissimilar. At their formation the conidia are unicellular, but

they may divide and become bicellular or multicellular. They are enveloped by a thick, dense wall and contain nutritive substances, especially of a fatty nature. In this state they can survive a long time.

Endospores or *gonidia* form in the interior of special spore-cases or sporangia, but not by a process of septation of the germinal hyphæ. When free and provided with organs of locomotion (flagella or cilia), they are known as *zoospores*, the spore-case giving origin to them being a *zoosporangium*. *Asci* are a particular form of sporangia, their spores being *ascospores*. The sporangium is frequently terminal and aerial.

Zygospores are products of a modified sexual act or a conjugation between two special hyphæ, either in the air or within some nutritive medium. These hyphæ send out small special branches, which come in contact, elongate, and take on club-shaped ends, by which they unite. A transverse partition forms at a little distance from each end of the united clubs, the original walls between them disappearing. The new cell now secretes a thick double wall, becomes charged with nutritive material, sometimes with pigment, and this resisting mass or seed is the *zygospore*. The special branches or *gametes*, the union of which produces the zygospore, are apparently similar, and it is impossible to discover a sexual differentiation.

Chlamydozoospores are asexual hibernating or resting spores with very thick walls, produced by an enlargement of special cells or branches. The membrane is pigmented and is charged with fat and glycogen.

Finally there are the *Oospores*, thick-walled resting spores borne by terminal or intermediate cells, resulting from a perfect sexual act or fertilization, and therefore strictly comparable with a fertilized ovum. The female element or *oosporangium* (*oogonium*) is provided with a thick wall pierced by pores, and contains one or more rounded masses of protoplasm (germ-cells, female gametes, or *macrogametes*). Fertilization is accomplished by the male gamete or *antheridium*, which forms on a thin special hypha and comes in direct contact with the oogonium, projecting a protoplasmic process into its interior, which fuses with it. In other cases the protoplasm of the antheridium separates into motile bodies (male gamete, *microgamete*, antherozoid, or spermatozoid), which approach the oogonium and fecundate it. In some fungal species, however, fertilization of the oogonium does not precede development, the transformation into an oospore being a process of parthenogenesis.

In a general way, the *life phenomena* of these higher pathogenic fungi resemble those of the bacteria, most of them being saprophytes in the free-living state, and depending on dead animal or vegetable matter for their nourishment. Parasitism in many cases seems an accidental acquisition, especially when the human host is chosen; but certain of these organisms have become well adapted to the parasitic mode of existence, and a few of the thread fungi have reached or approach closely the stage of obligate parasitism. But little is known of the mode by which these thallophytes produce the morbid processes with which they are associated, since they have not been so carefully studied as the bacteria; but, from the similarity of the lesions excited by their presence, it appears that some of them elaborate harmful toxic products, just as bacteria do. In other cases the lesions suggest that a mechanic effect, as by a foreign body, is the chief source of irritation to the invaded tissues.

In considering the individual parasites, two principal divisions of the

Thallophyta claim attention, viz., (1) the *Phycomycetes*, and (2) the *Mycomycetes*, to which must be added (3) unclassified pathogenic fungi.

Pathogenic Phycomycetes.—The phycomycetes are fungi resembling algæ, but destitute of chlorophyl. During active vegetation the mycelium is one-celled, remaining so in some cases, though generally becoming irregularly septate. Many species are aquatic. Reproduction takes place by sexual spores and by conidia or sporangia. Swarm spores (zoospores) occur in some species.

Phycomycetes are divided into three groups, with many families: *Chytridiæ*, or the zoosporous group; the *Oomycetes* or Oosporaceæ; and the *Zygomycetes* or Zygosporaceæ. No chytridiaceous fungi are known as human parasites.

The **Oomycetes** are divided into two principal families: the aerial *Peronosporaceæ*, comprising the mildews and white rusts, which are parasitic on the Phanerogamia, especially the Dicotyledons, and illustrated by the potato mildew, *Phytophthora* (*Peronospora*) *infestans*, or the mildew of the grape, *Peronospora viticola*; and the aquatic family *Saprolegniaceæ*, with three genera, *Achyla*, *Saprolegnia*, and *Leptomit**us*. Representatives of the first two genera are to be found in the dead bodies of insects falling in the water. *Leptomit**us lacteus* is found on submerged organic debris and in water-supply pipes, where it has been suspected of tainting the water.

Several species of *Leptomit**us* have been described by mycologists as occurring in the human body, some of which are placed in this category on meager grounds. Thus, *Leptomit**us urophilus*, found in urine; *Leptomit**us Hanoveri*, from the coating of esophageal excoriations; *Leptomit**us utericola*, from granulations in the cervix uteri; *Leptomit**us uteri*, from a uterine flux resembling pus; and *Leptomit**us oculi*, from the aqueous humor obtained by corneal puncture of an eye afflicted with rheumatic iritis. Some of these fungi probably followed accidental contaminations of the fluids in which they appeared, and it is questionable whether *L. Hanoveri*, *L. utericola*, and *L. oculi* belong to the genus *Leptomit**us*. A more common representative of this genus, presenting at least two varieties, is *Leptomit**us vaginæ*, which appears to provoke a mild chronic vaginitis, with itching and a discharge. In view of the recent discoveries of filamentous fungi (classed as *Sporothrix*) in refractory subcutaneous abscesses of the hand and arm, it is interesting to note the so-called *Leptomit**us epidermidis* (of Küchenmeister), discovered and described by Gubler, which form long, branching filaments, accompanied by ellipsoidal spores, isolated or in groups of two. This fungus was found in small white pustules which developed on the back of the hand and fingers of a young man, who had been shot through the hand, which was treated by continuous irrigation.

Among the **Zygomycetes**, several organisms of importance to the pathologic mycologist are found. The group is characterized by the production of resting spores (zygospores) from a process of conjugation in which two similar club-shaped hyphæ participate. Nonsexual spores or conidia, endospores or gonidia, and chlamydospores are also formed. One of the two principal zygomycetous families, *Entomophthoraceæ*, is parasitic in insects of various kinds, a familiar example being *Entomophthora muscæ*, the fly fungus, which is so destructive to the house-fly in the autumn.

The *Mucoraceæ* (or Mucors) constitute the other family of zygomycetes of interest to us, and they are typically represented by *Mucor mucedo*, com-

monly appearing on moist bread. They are widely distributed in nature, being chiefly saprophytic; a few only are parasitic. There are three principal genera: *Mucor*, *Rhizopus*, and *Montierella*; and Blanchard also includes the genus *Cercosphaera*.

Under ordinary conditions, certain species of mucors are nonpathogenic in man (*M. mucedo*, *Rhizopus stolonifer*). Others thrive at the body-temperature and provoke morbid conditions. Among these species are *M. pusillus*, *M. corymbifer*, *M. septatus*, *M. ramosus*, *Rhizopus racemosus*, and *R. rhizopodiformis*. In the first instance these fungi, which find their way into the body-cavities through the medium of air, water, and food, comport themselves as mildly harmful messmates. For example, *M. corymbifer* has been found on the arch of the palate, and a representative of the black moulds (*M. niger*) has been recognized as the cause of a chronic dark coating of the papillæ on the back of the tongue. The external auditory canal and the exposed face of the tympanum also furnish the habitat of certain species of mucor, as well as of *Aspergillus* (otomycosis). At other times the mucors participate in a more extensive local internal process, as in the case of pulmonary mycosis described by Cohnheim and Fürbinger (pneumomycosis). Finally there are cases of generalized mucor infection in which the spores are carried by the blood-stream, lodging in various parts of the body and forming mycelial filaments with the production of serious lesions. Such a case has been described by Paltauf, who made an autopsy in a case of death by coma after symptoms of enteritis and peritonitis, and found intestinal ulceration and hemorrhagic foci, focal pneumonia, cerebral abscess, suppurative laryngitis and pharyngitis, and splenic tumor, with the presence of a mucor (probably *M. corymbifer*) in the various lesions. *M. ramosus* has been found in the auditory canal, producing a very persistent brownish false membrane, causing earache and buzzing. Experimental general fatal mycosis has also been produced by the intravascular injection of spores of *M. corymbifer*, *R. rhizopodiformis*, *M. pusillus*, and *R. racemosus* into rabbits, with pronounced renal and intestinal lesions and less frequent involvement of the spleen and bone-marrow.

Cercosphaera Addisoni (Blanchard), variously described as *Microsporon Audonini*, *Torula vulgaris*, *Saccharomyces ovalis*, *Microsporon vulgare*, etc., is a curious fungus generally appearing as oval elements with drawn-out ends (gourd shape), about the size of an ordinary yeast-cell, and not forming a mycelium or chain of spores. During the reproductive phase the nucleus divides, probably by a process of karyokinesis, and by the successive divisions a considerable number of daughter-cells appear in the enlarged mother-cell. When placed in suitable fluid media, these daughter-cells become motile, flagellated zygospores. It is highly probable that these flagellate embryonic forms are the agents which penetrate the horny layer of the epidermis, from which arises the peculiar form of red or bronze pityriasis with which the parasite is associated. It was the bronzed hue of the infected skin that led to the confusion of this parasitic cutaneous affection with Addison's disease. This mycotic pityriasis is contagious.

Pathogenic Mycomycetes.—The mycomycetes are higher fungi, generally aerial, and having from the start a many-celled mycelium which increases in length by additions to the terminal cell, and are thus distinguished from the phycomycetes, which have a one-celled thallus that becomes septate only at the period of sporulation. Some of these fungi present a

comparatively simple organization; others become quite complex, some of the simpler forms doubtless representing underdeveloped examples of higher forms. They are divisible into four great groups: the *Uridineæ* or rusts, and the *Ustilagineæ* or smuts, which are parasitic on higher plants; the *Ascomycetes* and the *Basidiomycetes*, including the puff-balls and toadstools. We shall consider particularly the ascomycetes or sac fungi, which are characterized by the production of asci or ascospores, a mode of fructification equivalent to the formation of endospores in the sporangium. Fructification by conidia-like sprouts also occurs, taking a variety of forms. The ascomycetous fungi are separated into four orders: the Gymnoasceæ (including the Blastomycetes), the Perisporaceæ, the Spheriaceæ, and the Discomycetes. From the standpoint of pathologic mycology our interest naturally centers in the blastomycetes or yeasts, which occupy an important position among the pathogenic human parasites. As the type of this class of fungi, the familiar yeast of beer (*Saccharomyces cerevisiæ*) may be taken, and its morphologic and physiologic peculiarities will illustrate the biologic phenomena of blastomycetes in general. These organisms are round or oval cells with a cell wall of single or double contour and a protoplasmic internal mass, often containing granules and frequently exhibiting vacuoles. They are characterized by their method of propagation by budding during active vegetative existence—whence the name, budding fungi, applied to the order. Under unfavorable nutritive conditions or in the absence of oxygen, they multiply by the formation of endospores or *ascospores*. While generally unicellular plants, the yeasts are not invariably so, since the cells can elongate to form mycelial hyphæ; and at times a complicated ramifying septate mycelium is produced, especially when these organisms are grown in certain culture fluids, such as fluid beer-wort. At this time side buds, which separate into conidia-like bodies, may also appear on the hyphæ. While the property of fermenting fluids containing sugar is common among the saprophytic yeasts, it is not a universal function, being often absent among the parasitic forms.

Our knowledge as to the biology of the budding fungi is still meager, and for this reason a classification of the pathogenic species cannot be attempted. Indeed, it is quite probable that with further information some of the fungi now included in this order will be otherwise placed. For the present purpose, therefore, we shall content ourselves with briefly reviewing the blastomycetes described as pathogenic, retaining the nomenclature as at present applied. It is generally the custom to divide the blastomycetes into certain genera, *e. g.*, *Saccharomyces*, *Oidium*, *Monilla*, etc.

One species, classed with *Saccharomyces cerevisiæ* on insufficient grounds, has been found in the coating on the human tongue, in vomited matter, in diarrheal stools, in the vagina, and in diabetic urine. Neumayer believes that under certain conditions these organisms, which from their widespread occurrence easily find their way into the human alimentary canal, can produce diarrhea and flatulence. Other species of saccharomyces have been found in the purulent discharge of otitis media. Calmette observed yeasts in the blood, sputum, and urine of a case of typhus. An undetermined species of saccharomyces was also found by Troisier and Achalme in a pseudomembranous angina occurring in a patient suffering from typhoid fever, and this observation has recently been confirmed in other quarters. *Saccharomyces ruber* (Denme) of red raspberries has been held responsible

for the production of a family outbreak of intestinal catarrh, having contaminated the milk drunk by several of the children.

The most important communication on the subject of human saccharomycosis, and the one which has served to stimulate the present active study of this branch of mycology, is that by Busse, who in 1895 obtained pathogenic blastomycetes from a woman suffering with a peculiar cystic swelling of the tibia, which on histologic examination showed a sarcomatous-like structure of young granulation-tissue and giant cells. From the viscid fluid evacuated from the original tumor, and from the tumor-tissue, yeast-like fungi were obtained and isolated in culture. Thirteen months after the appearance of the tibial neoplasm the patient died, and at autopsy diseased foci, some reaching the size of an apple, were found in the lungs, kidneys, and spleen, in which the yeast organism abounded, lying singly or in colonies. A vesicle on the cornea also contained the fungi. The visceral lesions resembled those of a chronic inflammatory process with caseous and fatty degeneration, and contained an abundance of the parasites. Pure cultures of this yeast fungus were pathogenic for certain animals, particularly mice and rats, in which a chronic granulomatous neoplasm appeared about the injection-site, together with miliary granulation-tissue nodules in the lungs, kidneys, and brain. This organism grew well at room and incubator temperature on ordinary media, producing white, noncharacteristic cultures which did not liquefy gelatin. On special media to which malt extract was added, the growth was more profuse; and on prune-decoction and potato, grayish or even black cultures were produced. Acid media were especially suitable. Media containing glucose were fermented with the production of alcohol and carbon dioxid. Multiplication of this species occurred in the form of gemmation or budding exclusively, the production of endospores not having been observed.

Another blastomyces closely resembling that just mentioned is *Saccharomyces subcutaneus tumefaciens*, described by Curtis in 1896, and obtained by him from myxomatous neoplasms appearing beneath the skin of the thigh and in the neck of a young man, and also in a large purulent ulcer in the loin. The nodules were composed of a myxomatous tissue, richly cellular and resembling sarcoma. The yeasts were numerous both between the cells of the neoplasm and within them (blastomycetic cell inclusions). They were very easily cultivated, and produced ethyl alcohol and acetic acid in saccharose solutions. Rats, mice, dogs, and rabbits were susceptible to inoculations with cultures of this organism, a chronic infection with the production of multiple foci of subcutaneous inflammation and proliferation being provoked. Endosporous division was regularly observed in old cultures of this species. Corselli and Frisco also record a case of saccharomycosis in which tumor-like nodules (described by the authors as sarcoma) were found in the omentum and mesentery, and in which the yeast fungi were discovered in the chylous ascitic fluid obtained by exploratory puncture during life. The organisms were cultivated and found to be pathogenic for guinea-pigs, rabbits, and dogs.

From the morphologic resemblance of the blastomycetic nodules to tumors, and the fancied resemblance of the yeasts lying in animal cells to the cell inclusions appearing especially in malignant tumors, the blastomycetic theory of the etiology of tumors was promulgated in Italy by Sanfelice, Roncali, and others. That these investigators occasionally recovered yeast

fungi from true tumors seems undoubted, but their conclusions as to the etiologic relations of these organisms are apparently premature, since none of the species reproduced tumors entirely typical of those spontaneously arising in man; and of the various pathogenic blastomycetic species obtained from morbid processes in man or under saprophytic conditions, all failed to produce anything else than "pseudotumors"; that is, nodules of a chronic inflammatory character, containing enormous numbers of the yeast organisms in a granulomatous matrix. A careful experimental study of a series of wild yeasts was made by Rabinowitsch, who found several pathogenic species, some of which produced a septicemia, while others gave rise to granulomatous nodules.

Since the description of the first case by Gilchrist in 1894, we have learned that yeast fungi are also concerned in skin-affections (cutaneous blastomycoses) taking the form of a dermatitis (blastomycetic dermatitis), as

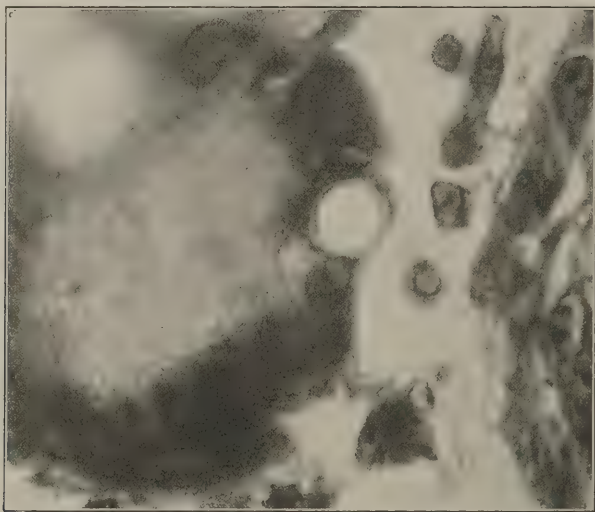


FIG. 97.—Blastomycetic dermatitis, showing a vacuolated blastomyces in the border of a giant cell. $\times 1200$. (Author's case; from a photomicrograph.)

noted in the cases of Gilchrist, Gilchrist and Stokes, Wells, Hektoen, and others. In Busse's case above noted, the skin in several regions became involved in an ulcerative process, from which the yeast fungi were obtained. The affection described by these writers takes the form of a chronic diffuse inflammatory affection resembling scrofuloderma or even lupus vulgaris. There is a marked epithelial hyperplasia, associated with the formation of giant cells and of miliary abscesses in the epithelium and subcutaneous tissue. Necrosis and ulcerative defects appear, and inflammatory granulation-tissue or scar-tissue may be formed to make good the defects. There seems to be considerable difference in the organisms thus far described in connection with these cases, and it is probable that at least two distinct species of the yeast fungus are concerned. Indeed, it is not impossible that one or more of these organisms, which produce well-marked mycelia, lateral buds, conidia, and pigment, may be found to belong elsewhere among the

fungi. Those which have been studied agree, however, in producing nodules of a chronic inflammatory character when injected into various animals, like the dog, horse, sheep, guinea-pig, rabbit, rat, and mouse. The inoculated animals generally pass into a state of marasmus, probably due to a slow toxemia, while the parasites which localize in favorable organs and tissues set up chemotactic and necrotic changes, followed by a process of granulation resulting in tubercle-like nodules. That suppuration may be produced by pathogenic blastomycetes has been determined experimentally.

Saccharomycosis of the mucous membranes is also possible, pathogenic yeast fungi having been obtained from cases of chronic catarrh of the uterine cervix by Colpe and Buschke, and from proliferative catarrh of the nasal mucosa by Busse. Saccharomycetes have also been found in the secretion from a case of peculiar inflammation of the conjunctiva and cornea.

Several diseases among the lower mammals are also ascribed to a blastomycetic origin, as, for instance, a farcy-like affection of horses (*lymphangitis epizootica*), characterized by a chronic inflammation of the lymphatics and lymph-glands, in which proliferation and nodular thickening are produced, later followed by a purulent softening. The parasite is probably identical with *Cryptococcus farciminosus* of Rivolta; it is smaller than *Saccharomyces cerevisiae*, and does not ferment sugars. And in guinea-pigs a pulmonary affection closely resembling tuberculous pneumonia is spontaneously produced by a species of saccharomyces (*Saccharomyces niger*, Maffucci and Sirleo), and the same species has been obtained from a spontaneous intestinal affection of guinea-pigs, localized especially about the cecum, in which thickening and ulceration of the mucosa were produced, with enlargement of the mesenteric lymph-glands and small nodules in the peritoneum. Epithelioma contagiosum of fowls and the so-called pox of doves are believed to be blastomycoses.

In the genus *Oidium*, tentatively included in blastomycetes, only one representative—long since recognized as associated with thrush—need concern us now, viz., *Oidium albicans* (Robin), also variously described as *Saccharomyces albicans*, *Monilia albicans*, etc. This disease is localized in the mucosa of the mouth, throat, esophagus, or more rarely in the epiglottis, trachea, bronchi, stomach, vagina, or nipples of nursing women. It is especially frequent in the mouths of infants, notably those in a marantic condition, and appears as a white or grayish membranous coating. Acidity of the secretions seems to be necessary to the progress of the disease, and the fungus *Oidium albicans* is very susceptible to alkalies. The organism appears both as spheric or oval budding cells and as tubular septate filaments, these filaments or hyphæ often ramifying to form a mycelium, from the elements of which buds continue to form. In certain media, as the liquid of Nägeli rendered saccharine, *Oidium albicans* produces endospores or ascospores, the minute spores being contained in a large thick-walled terminal cell (chlamydospore), also charged with glycogen. It is probably in this resisting stage that the organism survives and finds its way through the air or other medium to the oral mucosa of human beings. The organism penetrates the mucous epithelium, causing a swelling and desquamation of the epithelial cells; hyphæ also invade the underlying connective tissue, which responds to the irritation with a chronic small-celled proliferation. From these local foci the organisms may occasionally penetrate the blood-vessels, and thus be transported. Schmorl found miliary

abscesses and nodules in the kidneys of a child suffering from typhoid fever and oral thrush, and from these renal lesions and in the spleen he secured the oidium. In a brain-abscess following esophageal thrush in an infant, Zenker found the same organism. A systematic examination of the viscera of thirty-two individuals afflicted with thrush, made by Heller, resulted in the discovery of the fungus within the blood-vessels twelve times, and in thrombi six times. Experimentally it has been found that *Oidium albicans* causes a general mycosis similar to that produced by the pathogenic moulds.

Oidium subtile is the term applied by Blanchard to a fungus found by de Boyer and d'Antin (1881) in a pustular cutaneous affection of a cachectic infant, and it is regarded as identical with one described by Babes (1882) in an ulcerative dermatitis appearing on the abdomen and legs of a woman. The fungus resembled *O. albicans* somewhat, though its filaments were more slender. Terminal conidia arranged in linear series are formed; and while the mycelium branches at right angles, these branches are less numerous than in *O. albicans*. It is possible that some of the so-called yeasts of blastomycetic dermatitis belong in this category, and this is strongly urged by Giuseppe Cao.

Another species somewhat resembling the foregoing, but whose affinities have not been accurately determined, is *Rhodomycetes Kochi*, found by von Wettstein (1885) in the stomach in certain cases of pyrosis, where it formed a sporogenous fungus layer on the gastric mucosa.

The second ascomycetous order claiming attention is **Perisporiaceæ**,¹ which includes the fungi characterized by the formation of a mass of ascospores of varying numbers, arranged side by side to form a compact mass called the *perithecium*. Ordinarily this perithecial mode of fructification is not seen, the fungi developing asexually from a kind of conidial sporulation which is subject to various modifications. The order has been divided into *Erysipheæ*, represented by the blights to be found on various phanerogamia; *Tuberaceæ*, represented by the truffles; and *Aspergilleæ*, including a number of common moulds. *Aspergilleæ*, which concern us particularly, are represented by three genera, the first of which is *Penicillium*, which is typified by the blue-green bread-mould, and is characterized by a septate conidial hypha terminating in several short branches which swell into flask-shaped ends and give rise to a series of prickle-like extensions, *sterigmas* or conidia-bearers, each of which produces a linear series or chain of spores or conidia at its extremity, the whole fruit-bearing hypha with its sterigmas and conidia resembling a hair-pencil, hence the name of the genus.

The ordinary *Penicillium glaucum*, or bread-mould, has been encountered on the tympanum of the human ear, and in the dog it was found in a case of aural catarrh. Intravenous injections of suspensions of this mould produce a general fatal mycosis in rabbits, with the development of miliary, tubercle-like nodules in the viscera, together with mycotic emboli in the smaller blood-vessels.

A division of aspergillus, hardly of sufficient distinction to be classified as a separate genus, is *Eurotium*, characterized by the yellowish hue of its perithecia, which are delicate and easily distinguishable from the hard, woody sclerotium of aspergillus. Representatives of both this genus and subgenus

¹ It was formerly customary to include both Perisporiaceæ and Spheriaceæ under one order, *Pyrenomycetes*.

have been found to possess pathogenic properties either in spontaneous diseases in man or other animals or when used experimentally, the generic names *Aspergillus* or *Eurotium* being often used synonymously, as *A. flavus* (*E. flavum*); *A. fumigatus*; *A. subfuscus*; *E. glaucum* (*A. glaucus*); *E. repens*; *E. malignum*.

Sterigmatocystis resembles *aspergillus*, the species having been confounded at times. It is distinguished by the presence of basidia inserted on the flask-shaped end of the fruit-hypha, to which the sterigmas with their conidial ends are attached. Those of its species which are of pathologic moment are especially *S. antacustica* and *S. nidulans*. It is hardly necessary to say that inaccuracies still exist in the classification of *Aspergilleæ*, some of which have been but imperfectly studied by those able to determine their exact botanic position.

Aspergillar mycosis (aspergillosis) in man is not extremely rare. In a semisaprophytic existence (as commensal or lodger parasites) several species have been found in the external auditory canal, the tympanum, mouth, nose, maxillary sinus, throat, respiratory passages, eyes, genitalia. In several of these situations no apparent harm is done by the fungus. Thus aspergillar otomycosis is not an uncommon affection in apparently healthy persons with no appreciable aural symptoms; but at other times there is a serious purulent, fetid otorrhea, with more or less damage to the auditory mechanism. In such instances the mould fungi are usually associated with pyogenic bacteria, and are scarcely to be held alone responsible for the disease. Among the species encountered in the ear are *A. flavus* and *fumigatus*, *Sterigmatocystis antacustica*, *S. nidulans*, *Eurotium repens*, and *E. malignum*. Several cases of severe infection of the ocular mucosa with corneal ulcer and hypopyon are charged to the aspergillus group of fungi; in one such case described by Fuchs, the organism (*A. fumigatus*) also produced corneal ulcer when transplanted to the eye of a rabbit. Fungi of this group have also been found in a few instances of cutaneous disease, especially in a form of ulcerative dermatitis and in a peculiar kind of onychosis (onychomycosis), in which the epithelium of the nail-matrix exfoliates and prepares the soil for the aspergillus.

In the respiratory passages of man and other mammals, aspergillar mycosis assumes various types. The fungi sometimes are found developing on the mucosa of the trachea, bronchi, or even in the pulmonary alveoli without noticeable damage, apparently being only harmless lodgers. At other times pseudomembranous affections or necrotic changes and ulcerations of the respiratory tubes are found. But a still more extensive and serious affection is produced by these parasites, which was first recognized in pigeons, but afterward encountered in various mammals and in man. This is a form of pulmonary mycosis taking a tuberculous-like character (*pseudotuberculosis aspergillina*). In pigeons the disease attacks the mouth, lungs, liver, or kidneys, appearing either as a pseudodiphtheric affection of the mouth and air-passages or as a tuberculous affection of the lungs, with mycotic nodules in the liver and kidneys. Through the earlier studies of Potain, Diculafoy, Chantemesse, and Widal, and the subsequent observations of Renon, Gaucher, and Sergent, the interesting facts relative to the pulmonary mycosis of pigeon-breeders have been established.¹

¹ There is a class of individuals in France whose profession is the feeding of pigeons ("gaveurs de pigeons"), and it was a matter of popular observation that many of these

Aspergillar pulmonary mycosis¹ also arises from other sources, many of them inexplicable; and besides appearing as a primary infection, it may be secondary to other diseases of the lungs, the association of pulmonary tuberculosis and this mycosis having been noted. It is not entirely clear how the fungus provokes its pathogenic effects. The production of toxins has not been proved, and many maintain that the morbid tissue-reaction is merely the result of a foreign-body invasion. It is more probable that, as in the case of actinomyces, the pathogenic aspergillæ act both as foreign bodies and as producers of a mild toxin, to which the necrotic and leukotactic effects of their presence may be ascribed. Histologically the tubercles produced by these fungi resemble those of tuberculosis.²

The **Spheriaceæ** are ascomycetous fungi in which the spore-case or ascus is provided with an orifice for the escape of the spores. Most of the representatives of this order are saprophytes or are parasitic in other plants. The genus *Cordyceps* attacks certain insects; a related fungus, *Botrytis bassiana*, is the causative agent of the muscardin of silkworms, as Pasteur has shown. Certain species probably belonging to *Botrytis* have been found in human beings, as in a case of nasal catarrh by Schubert. Other spheriaceæ have been found in the auditory canal.

UNCLASSIFIED PATHOGENIC FUNGI.

Besides the fungi which have just been considered, the botanic relations of which are sufficiently well determined to admit of a system of classification, there is concerned in human diseases a series of microscopic plants the taxonomic position of which is uncertain. Some of these fungi have enough in common to be grouped together; but it is particularly with regard to their relations with bacteria and with the higher fungi just described that doubt exists. In many cases the lack of accurate data concerning the saprophytic life of these fungi is responsible for the difficulty. For the present purpose, however, only one course remains open; that is, to describe them together.

We shall first consider the **pathogenic ray fungi**, to which a number of organisms important in pathologic mycology belong, and which are characterized morphologically by a unicellular, branching, continuous or inter-

men were afflicted with a chronic pulmonary disease resembling phthisis. In examining the sputum from some of these cases, with the expectation of finding the bacillus of tuberculosis, small mycelial filaments were discovered instead, which by cultivation yielded a growth of *Aspergillus fumigatus*.

In this process of feeding ("gavage") of pigeons, a mixture of water and grain is insufflated into the bird's throat by means of a tube. In this manner direct contagion from the pigeon is rendered easy, though it is not certain whether the infection in man comes from the already diseased pigeons or from the particles of grain used in the feeding, which carry the spores of *Aspergillus*. The malady provoked by this infection takes a characteristic clinical course with some fever and emaciation, but it is chronic and not invariably fatal; in fact, some cases seem to recover entirely after several years of illness. The diagnosis is readily made by having in mind the occupation of the patient and by the discovery of the filamentous fragments of the fungus in the sputum. The organisms may also be recovered in culture or by the inoculation of animals, where a fatal aspergillus mycosis is produced, death resulting in three or four days in the pigeon after intravenous injection, or in six to eight days in the rabbit.

¹ See the monograph of Saxer (Pneumonomycosis aspergillina, Jena, 1899), and the paper of Pearson and Ravenel (*Proc. Path. Soc. Philadelphia*, new series, iii., 10, 1900).

² Oprüts and Moffitt (*Phil. Med. Jour.*, June 30, 1900) describe a pyemic process in a man, associated with a spore-forming mycelial fungus which exists as large round bodies in the lesions, but forms mycelium in cultures. A similar case is described by D. W. Montgomery (*Br. Jour. Derm.*, xii., 341, 1900).

rupted nonseptate mycelium, certain threads of which become spore-bearing. The individual filaments are quite straight, are bounded by a transparent membrane, and show a homogeneous internal structure during active vegetation. Sporulation is accomplished by a segmentation of certain of the mycelial threads to form conidia, and reproduction takes place from these spores or from fragments of the mycelium. True branching of the mycelial threads is a characteristic of these fungi. Various terms have been applied to the ray fungus group, the type of which is the organism of actinomycosis, and from the radiate threads of which the name is derived. Thus, they have been placed among *Cladothrix*, or so-called higher bacteria; they have been termed *Streptothrix*, from their twisted threads; *Oospora*, from their fancied resemblance to the *Oospora vulgaris* described by Wallroth; *Nocardia*, a noncommittal designation, after Nocard, who discovered one of the pathogenic species (that of a farcy-like disease of cattle); and *Leptothrix*.¹

It will be unwise, however, in describing individual members of the ray fungus group, to use the generic name *Actinomyces*, since this has not been fully sanctioned. The better plan seems to be to describe them under the specific names now commonly employed. In fact, it must be remembered that exact biologic data concerning a number of organisms in this group are still wanting, and that on further analysis some of them may be shown to be out of place in the ray fungus group.

Actinomyces bovis (*Nocardia* or *Oospora*), *Streptothrix actinomyces*, etc., are the terms by which the specific ray fungi of actinomycosis are known, which were first recognized and illustrated by Lebert in 1857. The disease in cattle was accurately described by Bollinger in 1877, and the human affection distinguished by Israel in 1882. There can scarcely be a doubt that several distinct species of actinomyces are capable of producing the clinical and pathologic picture of actinomycosis bovis and actinomycosis hominis, although it is impossible to define them sharply at present. As has already been indicated, *Actinomyces bovis* serves as the type of the ray fungi group, and, like most other representatives of its class, occupies an undetermined botanic position so far as its relation to other nonbacterial fungi is concerned. This indefiniteness is largely to be ascribed to lack of information as to the life history of these fungi under the saprophytic conditions in which they naturally exist.

As encountered in the tissues and secretions of infected animals, this fungus appears as tangled masses of threads, the ends of which make a kind of radiate figure or roset, and which are ordinarily visible in the form of small grains of a yellowish, red, or green color. At the extremities of the threads, particularly those of the periphery, pyriform or globular swellings are usually seen, while at other times nodular thickenings appear. The whole radiate mass is composed of this tangle of branching filaments constituting a mycelium, the filaments being sometimes composed of a succession of short rod-like structures. Originally it was considered that the bulbous extremities of these actinomycelial grains were spores; but this is not the case, though their exact nature is still undetermined, the most popular

¹ For a full discussion of the botanic position of these organisms, with an excellent bibliography, the student is referred to Hektoen's article, "The Classification and Nomenclature of the Ray Fungi," *Philadelphia Monthly Medical Journal*, November, 1899. To appreciate the confusion which has existed in the classification of these fungi, one should note the synonyms appended to the various species as described in some systematic work, as Blanchard's.

opinion being that they represent degenerative changes of the membrane bounding the terminal filaments. Cultures on ordinary media can be secured from these grains as they appear in the pus of actinomycotic lesions in man or cattle, although with some difficulty, since many of the masses are defunct. Growth is rather slow, but the surface of the solid medium ultimately becomes covered with a continuous furry layer, usually of a dirty white hue, but at times showing traces of yellowish, reddish, or black pigment. Gelatin is slowly liquefied. Ordinarily bouillon culture appears in the form of a submerged granular deposit on the side and bottom of the tube, but by certain manipulations a surface culture appearing as a velvety pellicle may be obtained. Here a process of sporulation may be observed, the aerial threads segmenting into a series of spheric or oval protoplasmic fragments, appearing in lines at the extremities of the projecting hyphæ. This production of conidioid bodies is the only process of fructification thus far observed among the ray fungi, and that it is a reproductive phenomenon seems undoubted from the facility with which new fungi develop from these "spores." A white surface layer on solid media is also significant of this mode of sporulation.

Actinomyces bovis passes its saprophytic existence principally upon cereals, and more rarely on certain grasses, where it probably flourishes as an oidium-like fungus comparable to the mildews. It is merely a facultative parasite, as must be evident from its inferior adaptation to this mode of life, being poorly equipped with destructive means like toxin-production, and also unable to find its way directly from host to host. Numerous recent observations leave no doubt as to the usual mode by which infection of man and cattle takes place, this being by contact with such grains as barley, rye, or wheat, or certain species of grasses. A particle of the barb of these cereals or grasses containing the ray fungi pierces the skin or finds its way into the respiratory or digestive tract, and from the traumatism which it provokes as a foreign body a nidus is made in which actinomyces grows.

Experimental inoculation with material from actinomycotic lesions or with cultures has given inconstant results. In most cases the reaction provoked by the inoculated fungus was nonprogressive, resembling that induced by an irritative, inanimate foreign body. Spontaneous infection is most common in the herbivora, especially cattle, but has been known to affect horses, swine, and dogs. It varies in its manifestations according to several modifying factors, such as susceptibility of the host, virulence of the particular species or variety of the fungus, nature of the organ or tissue attacked, and also according to the presence or absence of a mixed infection with pathogenic bacteria, which, in the case of the pyogenic cocci, is no rare incident.

Both an exudative and a proliferative tissue-reaction mark the invasion of the human organism by pathogenic ray fungi, the earlier and more frequent response being an exudate of a purulent character, later followed by the formation of granulation-tissue and scar-tissue. The reaction is a local one, and, compared with that of most other pathogenic vegetable organisms, a slowly progressive and mild one, due, no doubt, to the feeble or slightly toxic effects of the ray fungi. A round-celled infiltration, mostly of lymphocytes, is first induced, followed by the ingress of polynuclear leukocytes. Disintegration of the localized cells usually sets in early, with softening and the production of purulent foci. The outlying connective tissue responds to the irritation and a barrier of granulation-tissue surrounds the morbid area, and

in this tissue plasma-cells and mast-cells are abundant. Local extension is slow, seemingly dependent on the offshoots which grow in all directions from the original colony of ray fungi, and influenced by such factors as the nature of contiguous tissues, gravity, and the like. Phagocytosis, as in other infectious processes, is active about the foci of actinomycosis, and it is probable that vegetative portions of the infecting organisms are transported locally by this method, a supposition strengthened by the prevalence of degeneration among the cellular elements about actinomycotic lesions. Sometimes the production of new connective tissue is excessive, making neoplasms of considerable size, although the phenomenon is more common in cattle, where massive tumors of fibrous or osseous tissue mark the site of actinomycosis. At other times, either from the unusual chronicity of the disease or on account of the specific reaction to certain species of actinomycetes, a nodular process is set up, characterized by the proliferation of endothelioid cells, sometimes by giant cells, forming focal accumulations or nodules which tend to degenerate by caseous metamorphosis. At times both the exudative and proliferative phenomena may be seen in combination, and large fungous neoplasms with more or less suppuration are produced. In regions remote from large lymph-channels and vascular channels, the extension of the disease is usually slow; but both the larger lymph-channels and the blood-vessels may be invaded by the infective material, rapid metastasis being the result. This event is especially likely to follow the invasion of the larger veins, the lymphatic route being much less frequently selected.

Of the portals of entry for the actinomycetes, at least four are well known: the mouth and nasopharynx, the respiratory tract, intestinal tract, and skin (chiefly through wounds). At times it is impossible to discover the point of entrance (*cryptogenetic actinomycosis*). While infection is apparently possible through the direct transmission of actinomycetes or their spores through the medium of air, water, or soil, the more natural method is with particles of grasses or grain, on which the organisms pass their saprophytic existence, as carriers.

Streptothrix farcinica (*Nocardia* or *Oospora*) is the organism described by Nocard as the pathogenic factor in "farcin du bœuf," a nodular or tubercle-like affection of the superficial lymph-glands of cattle; nodules also occur in the viscera. The fungus appears as branching segmented threads joined in short sections, and Nocard claims to have observed the formation of conidial spores. Growth on culture media is in the form of a yellowish-white mouldy layer. It is pathogenic for guinea-pigs, cattle, and sheep, the mycosis usually taking the type of a pseudotuberculosis.

Streptothrix Forsteri is the fungus encountered in lacrimal concretions, which are largely composed of masses of the organisms. It has often been confounded with *Leptothrix*, especially *L. buccalis*, found as a coating upon teeth or as the agent of a pharyngomycosis. *Nocardia Hofmanni* and *N. Gruberi* are two species closely resembling the typical *Actinomycetes*, found as saprophytes, but also determined to be pathogenic for animals.

Nocardia asteroides (*Cladothrix* or *Oospora*) was discovered by Eppinger in 1890 in a cerebral abscess complicated with cerebrospinal meningitis, and appears as branching segmented threads, which are remarkable for the readiness with which they break into short quadratic fragments. The cultures are not distinctive, and the organism possesses no proteolytic property. Inoculations into rabbits and guinea-pigs produce pseudotubercles composed

chiefly of focal accumulations of leukocytes. The organisms obtained by Almquist, by Ferré and Faguet, and by Sabrazès and Rivière, from cases of cerebral abscess, resemble Eppinger's fungus. The same applies to a case of pleuropneumonia with subcutaneous miliary abscesses, studied by Rivière.

Streptothrix Maduræ (*Nocardia*) is the fungus of Madura foot, or mycetoma as Carter designated the peculiar disease of the feet and hands characterized by nodular foci, discharging a thick, fetid, puriform fluid, poor in pus-corpuscles, swelling of the affected members, and at times a necrosis of the bones. Peculiar yellowish or black granules found in the discharge were suspected by Ballingall in 1855 as being of parasitic origin, and this opinion was confirmed a few years later by Carter, who pointed out the resemblance of the grains to those of actinomycosis. Several instances of

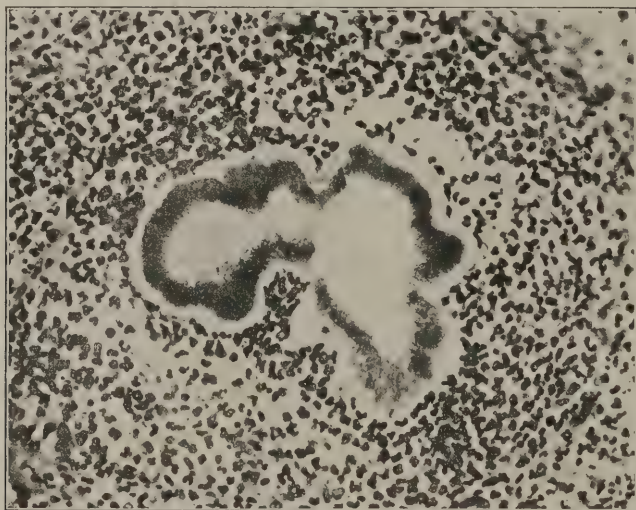


FIG. 98.—Mycetoma. Fungus surrounded by a dense accumulation of leukocytes. 300. (Dr. Hyde's case; from a photomicrograph.)

mycetoma have been observed in this country, principally in Texas. At least two varieties of the disease have been recognized by the color of the granules, the pale-yellowish or ochroid variety, and the black or melanoid variety.

Like those of actinomycosis, the ochroid granules of Madura foot consist of a mass of interwoven branching filaments or hyphæ radially arranged, making a mycelium such as seen in other ray fungi. These filaments are nonseptate, and the peripheral ones often show swollen or clubbed ends, though not invariably. Growth upon ordinary culture media occurs both at the room and body temperature, and the surface colonies on solids show a yellow, white, or even reddish color. Gelatin is not liquefied. In certain fluid media, like hay, straw, or vegetable infusions, this fungus grows especially well, forming a dense pellicle, from which the aerial hyphæ project,

the ends of which become sporogenous, giving rise to very resistant spores capable of propagating the organism.

The organism of melanoid mycetoma seems to be quite distinct from that just described, agreeing only in the formation of a dense radiate mycelium in the black granules. The filaments or hyphæ composing this mycelium are coarser than those of the ochroid fungus, more variable in size, and show both branching and lateral budding; they are also distinctly septate. On culture media the fungus grows rather slowly, producing a distinctly mouldy surface layer, from which aerial filaments grow in tufts. No production of conidia has been detected, the only approach to a process of fructification being a segmentation of some of the hyphæ in older cultures into a series of short segments. Wright, who obtained a growth of this organism, noted the formation of numerous black spheric granules in old growths, appearing in the midst of the mycelium and consisting of closely packed spheric or polyhedral cells, together with some short, thick, segmented hyphæ. The walls of these cells have a black appearance, and the granules seem to represent masses of interlacing, swollen, and much segmented hyphæ, and have been described as sclerotium. From the data thus far obtained, there seems to be little in common between the yellow and black fungi of mycetoma, and the latter seem quite remote morphologically from the ray fungi, having, as Dantec pointed out, closer affinities with mucor or aspergillus than with actinomyces.

Histologically the lesions of Madura foot are chronic and granulomatous, with atypical arrangement of lymphoid, epithelioid, and giant cells. At times an inflammatory reaction predominates, with accumulation of polynuclear leukocytes; and cavities, filled with pus-cells, endothelioid cells, and the débris of cellular necrosis, may form around the fungus granules. A boundary zone infiltrated with lymphoid cells and plasma-cells may form, and dense granulation-tissue is sometimes produced.

Nothing is known as to the saprophytic habitat of the ray fungus of mycetoma, in which parasitism seems to be an accidental acquirement for which it is poorly adapted, as evinced by the local confinement and chronic course of the disease in man, and by the failure of all experiments looking to its pathogenesis for animals. It is even less advanced in parasitism than *Actinomyces bovis*. The mode of its entrance into human beings is not determined, though the malady seems to follow a wound in the affected region. A prick, and particularly one by the thorns of *Acacia arabica*, an Indian tree, has been held responsible by certain observers, a view not improbable from what we know of the mode of entrance of *Actinomyces bovis*, although apparently refuted by the appearance of Madura foot in localities remote from the region where this tree is indigenous. Possibly, as in the case of other ray fungi, the fungus of mycetoma infests several different species of higher plants.

Streptothrix pseudotuberculosis is the designation applied by Flexner to a branching filamentous fungus discovered by him in 1897. The fungal threads appeared chiefly in the form of convoluted masses, some of which, as they terminated, showed imperfect partitions tending to break them into short rods. No cultures were secured, and inoculations of the pathologic tissue containing the threads into guinea-pigs were without result. In the man from whom the specimens were secured at autopsy there was a diffuse caseous pneumonic consolidation of the lung resembling a tuberculous affection, the

resemblance being heightened by the presence of miliary nodules consisting mainly of epithelioid cells, some of which were necrotic. Similar nodules were present in the omentum and other parts of the peritoneal cavity. Fungi apparently related to *S. pseudotuberculosis* have also been described by Buchholz, Scheele and Petruschky, and Larkin and Norris, all obtained from human lesions.

Before dismissing the ray fungi, it is well to recall the fact that some authorities now propose to include in this group all the pathogenic bacteria which show true branching, like *Bacillus tuberculosis*, *B. diphtheriae*, and *B. mallei*. In this same category doubtless also belong the acid-proof filamentous fungi which have recently been found in atypical cases of human pulmonary disease or by animal experiments, like the timothy, cow-dung, and grass bacilli of Möller, the butter bacilli of Rabinowitsch, the tonsillar bacillus of Marzinowsky, and an acid-proof bacillus recently obtained by Rabinowitsch from a case of pulmonary gangrene.

Besides these more pronounced pathogenic thread fungi which we have just described under the ray fungi, there are several organisms of recent discovery whose affinities have not been fully established and which may be here mentioned only as a matter of convenience. Thus, there is the fungus described by Cozzolino as *Bacillus filamentosus*, and obtained from a subcutaneous nodule behind the ear and from a retropharyngeal abscess in a young woman, appearing to the eye in the form of minute yellow or red actinomyceloid grains, growing well on ordinary culture media, and pathogenic for guinea-pigs and house-mice, producing in these animals pulmonary congestion and focal hepatic necrosis. In the tissue from the primary point of infection in the woman, the lesion resembled that of actinomycosis so closely as to merit the name "pseudo-actinomycosis," and the fungus was disposed in radiate filaments with clubbed ends. By cultural methods considerable deviation from the typical fungus of actinomycosis was shown, especially by the absence of branching, by the production of swarms of bacillary or spirilla-like rods, and by endogenous sporulation. It resembles more closely the anaerobic "bacilli" of pseudo-actinomycosis described by Sawtchenko and by Krassnobazew.

Another of these unclassified fungi is the *Sporothrix Schenckii* (Hektoen), a filamentous, sporogenous organism showing true branching and budding; it was obtained by Schenck (1898), and later by Hektoen (1900), from cases of chronic subcutaneous abscesses of the hand and arm, running a clinical course like farcy. The resemblance of this fungus to the meager description of *Leptomitosis epidermidis* has already been pointed out. In the infected tissues the organisms only appear as round or oval spores, not as filaments. They grow readily on ordinary media, and here a well-defined branching and budding mycelium of rather thick septate filaments is produced, from which spore-bearing or conidial threads radiate. The spores resemble yeast-cells and are able to reproduce the fungus. Experimental inoculations with the cultures were especially successful in guinea-pigs and white rats and mice, in which subcutaneous or intraperitoneal injections produced chronic circumscribed inflammatory and necrotic nodules accompanied by the formation of focal abscesses, closely resembling the lesions seen in the human being. This was more especially marked in subcutaneous injections in mice, in which the nodules coalesced and disintegrated, resulting in ulceration similar to that seen in patients.

In finally disposing of the unclassified pathogenic fungi, it is necessary to dwell briefly upon the organisms concerned in several parasitic cutaneous diseases (dermatomycoses). It will scarcely be profitable to go into minute details concerning these quite well-known fungi, or to attempt to describe the now considerable number of species differentiated by workers in this branch of mycology. Three of these cutaneous diseases and their parasites have long been known, viz., favus caused by *Achorion Schönleini*, tinea or herpes tonsurans by *Trichophyton tonsurans*, and pityriasis (tinea) versicolor by *Microsporon furfur*. Several subspecies of these three principal cutaneous fungi have also been described. The saprophytic existence of these fungi which in man induce affections more or less contagious is not determined, and their botanic position has not been established. The general characteristics of the dermatomycoses excited by them are a mild grade of inflammatory reaction, and hyperplasia of the epithelial elements of the skin. Scaly eruptions are in this way produced, some of which present characteristic colors. The fungi form extensive mycelia, which burrow in the superficial layers of the skin and along the hair-bulbs. In certain forms of tinea tonsurans, pus is produced along the roots of the affected hairs, or it may even affect the nonhairy portions of the skin, producing isolated pustules or purulent infiltration. The mycelial hyphæ of these fungi are septate, and all of them produce spores on special hyphæ resembling conidia. The organisms may be cultivated from their conidia on certain media, and reproduce simple or branching septate filaments which expand into the characteristic mycelia. Pyriform swellings appear on some of the threads, the significance of which is still undetermined. Some of these fungi have been successfully inoculated into animals, reproducing cutaneous diseases.

THE PATHOGENIC PROTOZOA.¹

Among the forms of animal life that have acquired parasitic properties are representatives of the lowest subkingdom, the Protozoa, a subdivision including those organisms which are unicellular in their fully developed state. The protozoa are minute single-celled organisms, existing either as independent individuals or as aggregations of similar forms.

Most of these animalcules are either free-living or saprophytic in their mode of life, and, compared with the fungi we have just discussed, relatively few of them are known to be parasitic in man. Of the few human protozoan microparasites, however, one particular class, represented by the

¹ Much of the literature on the pathogenic protozoa is to be found in the journals devoted to bacteriology and pathology, which have already been indicated. An elaborate systematic presentation of protozoa in general is to be found in Bütschli's *Protozoa*, Bonn's *Classen und Ordnungen des Thierreiches*, Leipzig, 1882. A more extended consideration of the pathogenic protozoa will be found in Leuckhart's *Die menschlichen Parasiten*, Leipzig, 1879; Blanchard's *Traité de Zoologie Médicale*, Paris, 1885; Braun's *Die thierischen Parasiten des Menschen*, Würzburg, 1895; Kruse's *Systematik der Protozoa* in Flüggé's *Die Mikroorganismen*, Leipzig, 1896; Blanchard's *Parasites Animaux* in Bouchard's *Traité de Pathologie Générale*, tome ii.; Moniez's *Traité de Parasitologie*, Paris, 1896; Pfeiffer's *Die Protozoen als Krankheitserreger*, Jena, 1891; Behla's *Die Amöben*; Balbiani's *Leçons sur les Sporozoaires*, Paris, 1884; v. Wasielowski's *Sporozoenkunde*, Jena, 1896; and Celli's *Malaria According to the New Researches*. Useful reviews upon various aspects of protozoan parasitology will be found in the *Ergebnisse der allgemeinen Pathologie* of Lubarsch and Ostertag; while in the English language the most exhaustive and valuable description of the malarial parasites in all the aspects presented by recent investigations will be found in the article "Malaria," by Marchiafava and Bignami, in the *Twentieth Century Practice of Medicine*, vol. xix., 1900.

organism of malaria, is of great interest and importance to pathologists, and it is not improbable that further knowledge will add to the list of pathogenic protozoa.

As to the place of these minute and chiefly aquatic animate forms in the organic scale, there has been some difference of opinion, since they approach closely the unicellular vegetable organisms and shade so insensibly into the multicellular animal forms as to make division difficult. In the case of those species with which the pathologist is concerned, however, no such difficulty arises, since these forms are far enough advanced in organization to make their animality undoubted.

Morphologically the protozoan exhibits a cell of varying shape, size, and structural complexity. This cell, which in mature forms is the animal itself, is composed of a protoplasmic interior, holding a nucleus well defined as such, or nuclear material dispersed throughout the protoplasm; while without, the protoplasm in all the higher protozoan forms is bounded by a definite external envelope, the cell-wall. Many protozoa are also provided with a dense external covering or shell, which may be soft and pliable or hard and calcareous. Locomotive organs, as cilia or flagella, are provided for many species. In the simpler representatives the protoplasmic mass composing the cell-body is undifferentiated, or at most composed of an outer clear portion (ectosarc) and an inner more dense portion (endosarc), this formless mass of living jelly constituting the entire organism; but in more advanced organisms, parts of the cell show a structural differentiation, some reaching that stage in which a definite aperture for food, another for excreta, and a distinction of the ends of the body exist.

The mechanism for obtaining food is generally simple, the protozoan merely enveloping the food particle by flowing its protoplasmic substance in such a manner as to surround and engulf the object. This mode of feeding is rendered possible by a kind of worm-like motility which the organism possesses, the so-called ameboid movement, by which it projects a portion of its substance in foot-like processes (pseudopodia), the bulk of the cell following by a curious forward flowing motion. In more specialized types, certain vibratile fibers or cilia develop a rhythmic motion, causing currents in the fluid medium by which food particles are drawn toward and into the food aperture. Certain vacuoles or spaces in the protoplasm serve to contain the food particles, while another system of vacuoles shows a kind of pulsation, appearing and disappearing at regular intervals, the so-called contractile vacuoles.

Reproductive phenomena in the protozoa take several distinct types, and even in a given species the character of the reproductive act may vary. Simple fission or direct constriction of the cell and nucleus of a mature organism into two new ones is the common asexual type. Sporulation is also frequently observed, the parent animalcule becoming enclosed in a dense wall (*encysted*), with or without sexual conjugation, and then dividing into minute protoplasmic particles taking a variety of forms, the so-called *spores*, which, on being set free under appropriate conditions, develop into mature organisms. Sporulation may be preceded by a fusion or conjugation of two apparently similar mature organisms, or a partial conjugation may occur in which the conjugating organisms only remain in contact temporarily until an interchange of nuclear material has been effected, then separate and multiply. Finally there is, even among these lowly animal

types, a distinct sexual process with well-defined male and female sex-elements and a process of fecundation or fertilization.

SPECIAL PATHOGENIC PROTOZOA.

Three classes of protozoa have representatives as human parasites: namely, (1) Rhizopoda, (2) Sporozoa, and (3) Infusoria.

Parasitic Rhizopoda.—The Rhizopoda (or Sarcodina) are protozoa which move about and feed by the aid of pseudopodia of various kinds, and reproduce by simple fission or budding. Most members of this class are provided with chitinous or calcareous shells. Only one of the four orders into which the rhizopoda are subdivided has been found as a human parasite: that is, the lowest or *Amœbina*, in which both naked and shelled forms are found; and of the genera into which this order is reduced, that of the simplest forms, or *Amœba*, contains the principal rhizopodal species of pathologic importance. As a genus, the *Amœbæ* are characterized by their short, blunt pseudopodia. Most of them have contractile vacuoles and nuclei. Reproduction takes place by simple fission in the active motile stage, or by encystment and sporulation in the resting stage. These organisms are chiefly aquatic—fresh-water or marine—although some species are found in the earth.

The most important parasitic member of the genus *Amœba* is *Amœba coli* of Loesch, also known as *Amœba dysenterie* from its association with this intestinal affection. Several species of ameba have been encountered in the human dejecta, apparently of no pathogenic moment; they have been found in association with other micro-organisms in diarrheal stools. The first exact description of intestinal amebæ was given by Loesch in 1875, who found them in the stools of a fatal case of dysentery. Somewhat later, Cunningham described ameboid organisms in the feces of cholera patients. Similar protozoa were noted by various observers, but it was not until Koch and Kartulis turned their attention to the subject that the causative relationship of these amebæ to tropic dysentery was suspected. This was in 1885–87, when several publications were made by these investigators, which were soon followed by a large number of confirmatory reports from various parts of the world, both in and out of the tropics.

As encountered in the dysenteric stools, *Amœba coli* is a large protozoon, a naked protoplasmic jelly from 8 to 37 mikrons in diameter, showing a clear outer ectosarc and a more dense and refractive endosarc. When alive and under favorable conditions of warmth it is actively ameboid, projecting one or two broad, blunt-ended pseudopodia, which at first consist of clear ectosarc, and into this the endosarc flows, imparting a progressive movement to the organism. The endosarc contains numerous fine granules and coarser bodies, among which red blood-cells, intestinal epithelial cells, and fecal particles may be recognized. One or more noncontractile vacuoles also appear in the internal substance, along with a vesicular clear nucleus in which a body comparable to a nucleolus may be detected in fixed and stained preparations. In the spheric, quiescent ameba, no differentiation of the protoplasm into endosarc and ectosarc is noted. A process of encystment is seen in intestinal amebæ, and Grassi has described the formation of minute bodies or spores which arrange themselves in the center of the cyst in a roset-like cluster, although this mode of reproduction has not been thoroughly substan-

tiated in the case of *Amoeba coli*. Simple fission is the ordinary reproductive method.

This ameba is constantly found in the stools of a particular kind of dysentery, which, from its regular prevalence in regions such as India, Arabia, and Egypt, is known as tropical dysentery. It is endemic in these regions, though not exclusively confined to them, cases of spontaneous origin having been repeatedly noted in the temperate zones. Besides appearing in the stools, the organism lies in the submucosa of the colon, usually at the base of the ulcerative defects characteristic of the affection. In the pus of complicating liver and pulmonary abscesses, the ameba also often abounds. In spite of the constancy of its presence, however, the precise etiologic significance of *Amoeba coli* is still unsettled. Many observers, of course, hold that it is solely and directly responsible for the dysenteric affection; but this is vigorously disputed by others, who call attention to the uniform association of pathogenic bacteria in the primary intestinal lesions of tropical dysentery, and to the impossibility of deciding how far pathogenic micro-organisms may be carried in the protoplasm of these protozoa, even when not otherwise transported. And there remains another difficulty in the way of a satisfactory demonstration of the specific pathogenicity of these parasites: that is, the practical failure of all attempts to secure them in pure cultures; so that experimental proof is wanting. Nothing is known as to the saprophytic habitat of the ameba; it is suspected that the organisms live in fresh water and effect entrance into human beings through drinking-water.

The *morbid effects* of the infection in which this protozoan parasite participates, either as the principal or as an accessory agent, are confined chiefly to the submucosa of the large intestine, where an edematous softening and necrosis mark the beginning of the disease. As the morbid process advances to the mucosa, this lining also becomes soft and necrotic, ultimately sloughing, and leaving the ragged undermined ulcers so characteristic of amebic dysentery. The amebæ first appear in the submucosa, and, when the process has advanced to the stage of ulceration, these organisms may be found in the material filling the ulcerative defect, in the regenerating submucosa making the floor of the ulcer, and also in the apparently unaltered submucosa remote from the principal lesion. In sections of well-fixed tissue containing amebæ, they may be readily recognized by virtue of their metachromatic staining reaction with thionin, used after a special process (Mallory), or by the use of toluidin-blue (Harris). Apparently the presence of the ameba is not capable of exciting a chemotactic inflammatory reaction, and where suppuration occurs it is usually ascribed to mixed infection with pyogenic bacteria, as Councilman and Lafleur have shown in their thorough studies of amebic dysentery. A moderate infiltration of lymphoid cells and occasionally a proliferation of large endothelioid cells are the usual reactions provoked by these organisms. It is still undetermined how these protozoan parasites find their way into the submucosa, where they first appear, without demonstrable lesions of the mucosa, the most probable view being that they penetrate through the intact mucosa from the contents of the bowel, evidently finding in the submucous layer the proper soil for their pathogenic activity.

Liver abscess, usually solitary, sometimes multiple, is the most frequent secondary lesion of amebic or tropical dysentery, and here the characteristic ameboid organisms are often, though not always, found alive and generally numerous in the material from fresh abscesses. In small beginning abscesses

the process is particularly a necrotic one, in which the parenchymatous cells of the focus are disintegrated with little or no inflammatory exudation; and even in the large abscesses the contents are not ordinary pus, but a puriform, chocolate-colored fluid resembling anchovy sauce and containing detritus and amebæ with few leukocytes. Two methods of transportation are believed to be operative in the production of amebic liver abscess: one by the portal venous route, the amebæ penetrating the venous radicles in the affected intestines; the other by direct penetration of the colon and passage across the peritoneal surfaces to the liver, rendered relatively easy by the close proximity of the hepatic flexure of the colon to the liver.

From the studies by Quinke and Roos, which were a continuation of those inaugurated by Kruse and Pasquale, it has been discovered that it is possible to reproduce an ulcerative colitis in cats, by rectal injections of material containing amebæ, either the dysenteric stools or fluid from amebic abscesses, or of material from apparently healthy persons after a saline purge. It appears, however, that not all examples of amebæ tested in this way are uniform in their pathogenic activity; and from the results of these experiments and a consideration of the morphologic characteristics of the organisms, the authors first mentioned have endeavored to differentiate three species of parasitic intestinal amebæ, as follows:

(a) *Amœba intestini vulgaris*, 40 mikrons in size, coarsely granular, pathogenic both for man and the cat.

(b) *Amœba coli mitis*, morphologically similar to (a), but pathogenic for the cat alone.

(c) *Amœba coli* (Loesch), 25 mikrons in size, finely granular, pathogenic both for man and the cat and provoking dysentery in both.

Among the nonpathogenic amebæ apparently living in a state of commensalism in the human intestine, several imperfectly classified species have been described; and in the oral cavity, especially in the tartar on the teeth, several observers have discovered ameboid organisms, although it is unknown whether these really represent protozoan species or are developmental stages of some plant form.

Amœba urogenitalis, Baelz, 1883, is the title of a rather large (50 mikrons), actively motile rhizopod, which was found in the bloody urine and in the vagina of a 23-year-old woman dying of pulmonary tuberculosis, who, shortly before death, developed hematuria and extreme vesical tenesmus. Morphologically this animalcule closely resembled *Amœba coli*. Baelz was of the opinion that infection occurred first in the vagina, probably through washing with dirty water, the urethra and bladder being secondarily invaded. Jürgens describes the bladder of a man in which he found mucous cysts filled with amebæ, although no symptoms directed attention to this condition during life. Kartulis found amebæ, smaller than those described by Baelz, in the bloody urine of a man suffering from vesical tumor; and Posner records a case of sudden chills and hematuria in a patient, in whose urine large ameboid organisms were present, along with renal cells and tube-casts. The attack was repeated several times after the subsidence of the first one, the urine being free from blood in the interval. Posner thought a direct causative relation could be established between the amebæ (which he believed to have travelled from the bladder to the pelvis of the kidney, there becoming encysted), and the urinary disease.

As having a possible connection with the amebæ found in the oral cavity, the cases noted by Flexner and by Kartulis may be mentioned. The first-named observer found small, actively ameboid organisms in the pus evacuated from an abscess beneath the chin, which followed the excision of a nodule beneath the gum of the lower jaw, an ulcer remaining after the extirpation. The lesion was encountered in an old man, and in the fetid pus various bacteria were also present. Kartulis found amebæ measuring 30 to 38 mikrons in diameter in the pus and in a piece of exfoliated bone from a fistulous opening into a tumor-like mass the size of an orange, situated beneath the lower jaw of an Arab. No distinction between an endosarc and ectosarc was noticeable in the first-mentioned organism; but in the one described by Kartulis these portions of the ameboid body were well defined, and blood-cells and pus-cells could be distinguished in the coarsely granular endosarc, together with vacuoles and a stainable nucleus.

Pathogenic Sporozoa.—It is rare indeed to find all of a large class of organisms exclusively parasitic in their manner of life; but such is the case with the second protozoan class, which are now to be discussed—the Sporozoa. So far as is now known, not a single representative of this extensive group of unicellular animal organisms is free-living. Many of the sporozoa are, however, innocuous parasites; but others are capable of exciting pathologic changes or inducing death in the host. With the possible exception of Cœlenterata, none of the animal subdivisions above protozoa are exempt from sporozoan parasitism. From the pre-eminently predatory mode of life, a high grade of adaptation to parasitism is to be expected; this is precisely what we find in the sporozoa. Many of them are so minute in the adult condition as to enable them to exist within the cells of their animal host, sometimes in numbers. Having no occasion to obtain food by foraging, the adult sporozoon is not ameboid, but in most cases is provided with a dense external cuticle. Nutrition is secured by direct absorption of the juices of the host. A pulsating vacuole, such as is seen in the ameba, is not found. Although strictly unicellular organisms, certain sporozoa show a remarkable cell differentiation—an adaptation for greater security in their parasitic habits. This is illustrated in the case of certain Gregarinæ, in which the unicellular elongated body is divided into two portions by a partition: the posterior one or deutomerit, and the anterior one or protomerit, which is drawn out and again partitioned to make two parts, of which the pointed terminal one is the epimerit; this is furnished with hooks or other apparatus for attachment to the tissues of the host. The method of reproduction which obtains among the sporozoa is that best suited to further parasitism, being a process of encystment and sporulation with the production of spores, generally very small and well endowed with dense external layers or shells, by the aid of which the stress of extracorporeal existence is long endured.

These organisms vary widely in size. There is one species of Gregarina, an inmate of the intestinal canal of the European lobster, which attains a length of 16 mm. in its adult condition, and the spore cysts of which in the lower intestine of its host are as large as the head of a small-sized pin. This *Porospora (Gregarina) gigantea* is one of the largest unicellular organisms known. On the other hand, exceedingly minute forms abound among the sporozoan species, some taxing the extreme range of microscopic vision; and it is by no means improbable that, as in the case of recently studied bacterial organisms, there may be sporozoan parasites the spores

of which, as they abound in the tissues and juices of the animal host, are entirely beyond the range of our present optical appliances.¹

There is a wide range of morphologic diversity among the sporozoa, and thus generic and specific distinctions have been drawn until this class of protozoan organisms has become a very numerous one. But in the life history of a given species the morphologic phases are also diverse, complicated, and in many instances but imperfectly understood; in view of which the classification of these, as of so many other micro-organisms, is difficult. On the whole, it is not surprising to find that considerable discord reigns among the writers occupied in this trying field of microparasitology.

It was for a long time believed that all sporozoa were asexual in their mode of reproduction, the only exception to a strictly nonsexual process being the conjugation between certain Gregarinæ, which preceded encapsulation and sporulation. But recent discoveries controvert this notion, a remarkable sexual process with a high order of preparatory steps having been proved for certain Coccidia, and a more simple one for certain Hemosporidia, so that it now appears more than probable that further study will discover sexual reproduction as a prevailing phenomenon among these lowly forms of animal life; and when the reproductive stages of the various representatives have finally been worked out, an entirely new basis of classification may be secured, probably changing radically the system now in vogue.²

¹ It is perhaps opportune to recall in this connection that there is a series of human maladies with decided impress of an infectious nature, in which no parasitic agency has been positively demonstrated. For example, the acute exanthemas, the contagious nature of which has been known for centuries, like *small-pox*, *scarlet fever*, *measles*, *chicken-pox*, and exanthematous *typhus*, are classed among this group of morbid affections. *Rabies* is a still more remarkable illustration. Now the morbid anatomic and histologic analogies of these diseases are such as to suggest their identity with many well-known and positively determined microparasitic affections, and the biologic (clinical) phenomena which they exhibit are similarly suggestive. We are therefore forced, for the present at least, to place them in a category of infectious diseases the specific parasites of which still remain to be discovered. Since the bacteriologic era, all of these diseases have been studied by the same methods which have yielded such brilliant and positive results in a large class of infectious maladies, and many microbic organisms have been heralded as specific excitants; but even at this time there is no case in which a reasonable scientific conservatism allows acceptance of the claims of those who profess to have made these discoveries. The failure of bacteriologic methods in a class of diseases so obviously infectious has long since directed the thoughts of parasitologists in other channels, and many have looked to the unicellular animal organisms—the protozoa—in the hope of there finding the etiologic agents. For the exanthemas, at least, this view, first proposed by prominent bacteriologists like Robert Koch, seems entirely probable, especially when we recall how barren are the attempts to cultivate artificially or to inoculate successfully the parasitic protozoa, how extremely small many of them are, and how roundabout the means by which they often obtain access to the human host. With the suggestions offered from sources of such authoritative prominence, it is but natural that the field of protozoan parasitology as related to these particular diseases should have been well explored, and with the consequence that several observers profess to have discovered unicellular animal parasites in *small-pox*, *measles*, *chicken-pox*, etc., in the blood, in the organs, or in the cutaneous lesions—claims which, like those of L. Pfeiffer, are much too positive.

Among other diseases of obscure etiology, leukemia may be mentioned as one in which protozoan parasitism has been suspected, a view at present strongly urged by Löwit.

² The studies upon sexual phenomena among sporozoans which have attracted special attention are those by Simond, Schaudinn and Seidlecki, and by Seidlecki (from whose paper, "Etude Cytologique et Cycle Evolutif de *Adela Ovata* Schneider," *Annales de l'Institut Pasteur*, xiii., 1889, the following data are obtained), upon *Adela ovata* and *Coccidium* (*Eimeria*?) *Schneideri*, two coccidia infesting the intestinal epithelium of *Lithobius forcipatus*, one of the Myriapoda. These observations are extremely interesting, and have been carried to that stage of completion that makes them models for future work along this direction.

Adela ovata is, in the adult intracellular condition, a large ellipsoidal organism, from 40 to 50 mikrons in length by 16 to 22 mikrons in width. Its protoplasm shows an

Therefore, as has so frequently been the case with reference to other organisms belonging to the great group of microparasites, we are compelled

alveolar structure and uniformly distributed fine granules. The external portion of the parenchyma forms a cuticular membrane. A spheric nucleus lies in the center. Within the nucleus are distinguished a karyosome and several filaments, and chromatin granules also appear on appropriate staining. This, which is now known to be the adult female form (*female gamete*), attains its full size and then proceeds to undergo a complicated process of nuclear division by which the mother-nucleus disappears and a series of chromatin particles are diffused in the protoplasm, at first condensed, but soon expanding into star-shaped figures, the organism at the same time becoming globular and its protoplasm condensed. The chromatin stars move to the periphery of the cell and contract into a dense oval reticulum, while about each of them the protoplasm segments until a series of oval nucleated bodies are produced; these elongate, become separated, and, to the number of twenty or more, appear as slightly bent, sickle-shaped, nucleated filaments, which on final detachment are motile. These bodies, arising from the segmentation of the gamete, are the *macrogametes*; they escape from the cell in which the adult parasite lay, finding their way into the lumen of the intestine. By virtue of their motility and their falciform shape, these segmentation forms can again penetrate the epithelial cells of the intestine, thus bringing about a reinfection of the host. Arriving in the cell, the falciform body becomes oval and gradually assumes the adult condition, to repeat the process of division just mentioned. This *asexual mode* of reproduction continues for some time.

Now, besides this larger adult form, there is a smaller oval one, with more compact, non-vacuolated protoplasm containing several small brownish masses of pigment. Its nucleus is relatively large, the chromatin is condensed into a close network, and a large karyosome with several vacuoles lies in the center. By its smaller size, its granular protoplasm, relatively large nucleus, this *male* parent cell, or *male gamete*, can be distinguished from the one just described. It grows to full size, when a process of nuclear division with preliminary division of the karyosome and dispersion of the chromatin appears, the globular cell finally dividing into meridional sections, each of which contains a compact nucleus and fragments of pigment. These sections ultimately separate into crescentic forms, which are parent male cells or *microgametocytes* ("microgamétocytes"); they are endowed with extremely active motility, and, on escaping from the harboring cell of the host's intestine, they swarm about in the lumen, again entering epithelial cells to become adult and divide by the asexual process. From this it is apparent that *auto-infection* of *Lithobius forcipatus* takes place by the *asexual reproduction* of *dimorphic representatives* of *Adela ovata*, which may be differentiated as female and male; and, so far as this host is concerned, such asexual method of reproduction is sufficient for the parasite. But it will be evident that this process makes no provision for the perpetuation of the sporozoan species in event of the death of the host, nor does it provide a means for the parasite to infest other representatives of this species of Lithobiidae. For this contingency and to give rise to a well-endowed resisting stage, another means of reproduction is called into play; that is, a *perfect sexual process*, the product of which finds its way from the intestines of the host into the outer world, there prepared to await a favorable moment for again entering a new host.

The sexual phenomena observed in *Adela ovata* are remarkably complicated when it is remembered that this species is only a lowly protozoan organism. It happens thus: Some of the macrogametes, instead of again entering the cells of the host, remain in the lumen of the bowel, there to become fully developed forms. In like manner, certain microgametes remain free. So far as the female cell, macrogamete (or even *ovum*, as we may now call it), is concerned, it is prepared for the act of fecundation except for a *process of maturation* or ripening, which appears actually to occur even in this lowly form of animal life. Preceding the maturation, a microgametocyte approaches the macrogamete and fastens itself to one pole, then the nucleus of the macrogamete recedes either to the opposite pole or to the one against which the microgametocyte is applied, and soon expels a particle of chromatin which escapes from the surface of the coccidium. Meanwhile an important transformation is going on in the microgametocyte, the nucleus of which goes through a division process giving rise to figures somewhat like those seen in karyokinesis, even to the production of a chromatic particle between the receding masses of nuclear substance (believed to be analogous with the "Zwischenkörper" seen in metazoan cells), and finally four elongated, somewhat pyriform bodies, composed almost or entirely of compact chromatin, are formed. These are the male reproductive elements, the *microgametes*; or, in other words, the *spermatozoa*. In the living state they are highly refractive and motile, though non-flagellate. Only one of these microgametes now penetrates the macrogamete at the pole in which the remainder of the nucleus lies. When the ripened nucleus of the macrogamete adjoins the pole to which the microgametocyte was attached, one of the spermatozooids enters directly; but when the female nucleus lies at the opposite pole, the microgametes travel around the female cell to reach this point. Here we have a perfect act of fecundation or fertilization, preceded by reducing divisions of both the male and female sexual cells. And as in fertilization among higher animal forms, so here the male and female chromatin filaments can be identified for a short time in the fecundated cell.

to accept as only provisional many taxonomic features now applied to the sporozoa.

Of the several systems of dividing the class Sporozoa, that making six orders has been most widely accepted, and is as follows :

Order I., **Gregarinæ**, single-celled, round, oval, or elongated organisms, some of large size, as has already been noted. Some have unpartitioned cell bodies (Monocystidæ); in others the body is divided into two or three segments, of which the anterior becomes specialized into a proboscoidiform attachment-apparatus (Polycystidæ). Parasitic in invertebrates (Echinoderms, Annelids, Arthropods, and Vermes). Reproduction by spores, the germinal portions of which consist of falciform protoplasmic rods.

Order II., **Myxosporidia**, sporozoa the adult stage of which is characterized by the presence of nuclei originating by division, further by the power of ameboid movement and by the mode of spore formation, which takes place in definite transparent areas (pansporoblasts), and which is progressive, not being confined to the last stage of the life cycle; the spores always exhibiting two, and sometimes three, axes of symmetry and possessing a shell resistant to chemical reagents, one or more capsules (each inclosing a coiled filament capable of extrusion), and a single mass of sporoplasm.¹ Parasitic in several invertebrates and also among fishes, where they often work great devastation, and in batrachians (only two or three species) and in reptiles (crocodile?).

Order III., **Coccidia**, are principally intracellular parasites, choosing especially the epithelial cells of the intestinal mucosa, although at times lodging between the cells of the intestinal submucosa or in lymph-glands, liver, etc. They are round or oval bodies, germinating by falciform spores formed within the parent cell, which becomes invested with a protective envelope; this mode of asexual reproduction takes place within the infected cells of the host, but another sexual process takes place outside of such cells, the product of this act dividing into a series of sporocysts which are the resisting stage of the coccidia, through which it infects new representatives of the host species. Each sporocyst contains two or more crescentic germinal bodies (*sporozoites*), which, when set free in a new host, penetrate suitable cells and establish a new generation.² Parasitic in certain invertebrates, like molluses and arthropoda, and in birds, reptiles, and mammals, including man.

Among the mammalian coccidia the species best known is *Coccidium*

Following fertilization the impregnated nucleus of the cell is carried again to the surface, where the chromatin network becomes more compact, elongates, and divides into two portions, with the appearance of two "Zwischenkörper" in the uniting filament. This division or segmentation is repeated, the protoplasm following, until a series of aggregated round cells with a bounding membrane is produced, which are the *sporocysts*. Finally, within each of these sporocysts the protoplasm condenses and divides into two small elongated, curved rodlets, each of which contains a nucleus; these are the *sporozoites*. Escaping from the original host, some of these sporocysts finally find their way to the intestinal canal of another like myriapod, where the two sporozoites are set free to commence a new cycle.

¹ This definition is from Gurley, "The Myxosporidia, or Psorosperms of Fishes, and the Epidemics Produced by Them." From *Report of the U. S. Commissioner of Fish and Fisheries*, for 1892. This article, containing a detailed systematic description of 102 myxosporidian species parasitic in fishes and batrachia, is readily accessible to American students and should be consulted by those who would look more closely into this extremely interesting class of parasites.

² This description of the alternate generations and complex life cycles of Coccidia is founded on the observations of Simond, Schaudinn, and Seidlecki, in a few species (see description, p. 305, footnote). In all probability it applies to coccidia as a whole, with modifications for the individual species.

oviforme, especially common as a parasite in the epithelial cells of the bile-ducts and liver of the rabbit. In its encysted state this organism is oval, 33 to 40 mikrons long and 15 to 28 mikrons wide, surrounded by a double-contoured dense capsule, within which is a coarsely granular cytoplasm which contracts into a central sphere, afterward dividing to form four spheres which become ellipsoidal, encapsulated, and which are sporocysts ("sporoblasts"); in them are produced two nucleated falciform bodies with an enlarged knob-like end, the *sporozoites*. These sporocysts, as in other coccidia, are the resisting forms of the parasites, which develop in the extruded stools of one host to infect the food and re-enter a new one. Besides this mode of reproduction (which is probably sexual), *Coccidium oviforme* shows another (asexual?) reproductive process in which a parent intracellular coccidium (called "Schwärmercysten" by L. Pfeiffer, who first described the process) divides into a large number (eight to thirty-six) of small sickle-shaped motile spores, which swarm into the intestinal canal and from which reinfection of the host occurs. It was this phenomenon that in 1892 led R. Pfeiffer to venture the prediction that this species had two evolutionary cycles, one endogenous and the other exogenous, a prediction which has been fulfilled in the case of the coccidium *Adela ovata*, for example, as we have already seen.

In man, infection by *Coccidium oviforme* has been observed several times, although some of the accounts are of questionable authenticity. Gubler described the case of a man with enlargement of liver due to tumor-like nodules, which on autopsy proved to be cysts with caseous, semipurulent contents showing numerous oval bodies, which were at first regarded as distoma eggs, but which Leuckart thought to be coccidia. Somewhat similar cases of liver affection were reported by Dressler, Sattler, and Perls. Virchow noted a similar case in 1860, but thought the oval bodies to be eggs of *Pentastomum*. More recently Podwysoski described extensive coccidiosis of the liver in four cases examined by him, but his investigations are of questionable value and not generally accepted as trustworthy. In Silcock's case the parasite was carefully examined, and it probably belonged to *Coccidium oviforme*; it was found in the liver of a woman, who presented obscure typhoid-like symptoms before death; at autopsy numerous caseous foci were found in the liver, which were identified as coccidial nodules. Haddon also reports a somewhat similar case in which coccidial nodules were scattered in the peritoneum, omentum, liver, kidneys, spleen, and pericardium.

Another species, *Coccidium perforans*, also found in the rabbit, has also been apparently identified in the stools of human beings. The organism was found in the feces of a mother and her child, who had both been suffering from a chronic diarrhea.

Coccidium bigeminum, found by Stiles in the intestinal epithelium of the dog, has been detected occasionally in the intestines of man.

Several cases of coccidiosis of the kidneys and ureters due to undetermined coccidia have been described. In a purulent pleural exudate obtained by puncture, Künstler and Pitres also found coccidia-like bodies.

Order IV., **Sarcosporidia**, are elongated, relatively narrow organisms, the habitat of which is between the muscle-fibers or muscular fascia of a number of vertebrate animals, including man. As "tubes of Miescher" or "of Rainey" they have long been known, having been described in the domestic

mouse by Miescher in 1843, and in swine by Rainey in 1858. The adult form presents rounded or pointed ends and attains a varying length in the different species, some of which are remarkably large for unicellular organisms. Reproduction takes place by a process of sporulation in which great numbers of reniform or falciform spores are produced. These are considered as equivalent to the sporozoites of *Coccidium*, but the life cycle of the sarcosporidia has been but imperfectly worked out, and nothing is known of the mode by which infection occurs. L. Pfeiffer believes an intermediate host is necessary to transport the sporozoites.

Lindemann and Rosenberg record cases in which sarcosporidia-like masses were found in the human heart. The observations are imperfect. A more probable case is that reported by Kartulis, who found Miescher's tubules in the abdominal muscles and in the abscess-cavities of a man who died of multiple liver-abscess and abscess of the abdominal wall; but even here the identity of the bodies described as sarcosporidia is doubted.

Order V., **Microsporidia**, are minute sporozoa infesting the epithelial cells or muscles of arthropoda particularly. They are generally encountered in the spore stage, invested with a thick shell which opens to give exit to an ameoboid body; this finds its way into epithelial cells or other favorable sites, there to enlarge, encapsulate, and divide into numerous small spores by which auto-infection of the host is produced. These organisms are particularly notorious as the cause of pébrine disease of silkworms, having worked sad havoc to the silk industry of France and Italy by inducing extensive epidemics. Pasteur, who investigated this disease, found that the eggs of an infected female silkworm conveyed the microsporidian spores to new generations, and he suggested a satisfactory mode of prevention, consisting in the examination of the eggs and the destruction of those found infected.

Order VI., **Hemosporidia**, include the most important protozoa parasitic in the human being, viz., the organisms of malarial fever. It is a large sporozoan family of blood-parasites, as the name indicates; that is, of parasites which pass at least one stage of their existence in the red blood-cells of certain vertebrate animals, among which are numbered reptiles, amphibia, birds, and mammals. At the present moment it is important to emphasize the statement that the hemosporidia pass but *one stage* of their life cycle in the blood of a vertebrate host, for, in several of the members of this order infesting warm-blooded animals, it has been proved definitely that the parasites have *another life cycle*, passed in the body of some insect. As we have already seen in the case of *Adela ovata*, and as is suspected to be the case in *Coccidium oviforme*, the hemosporidia of warm-blooded animals, at least, have an alternation of generations, with this important difference; that whereas the second life cycle of the designated coccidia is extracorporeal, that of the hemosporidia is intracorporeal—in the body of an intermediate host.

Several attempts have been made by zoologists to classify the hemosporidia thus far discovered, but an unobjectionable system has not been found; and with the mass of new facts that are now accumulating with reference to the complete life history of this group of organisms, a new system is in process of construction. It appears more to our purpose, therefore, to pass over this phase of the subject and to describe the individual hemosporidian organisms, particularly those of direct or indirect importance in

human pathology. To this end, we shall consider two subdivisions: (a) hemosporidia of birds, and (b) hemosporidia of mammals.

Hemosporidia of Birds.—In discussing these organisms, at first sight belonging strictly to the domain of comparative pathology, a word of explanation should be offered. It is chiefly through the data gained in this field that our knowledge of the malarial organism of man has been enriched, and the organisms concerned in these avian infections are so readily accessible for study and so characteristic in their biologic phases that every student in this field of pathology should personally verify the facts already gathered, either as a preparation for or sequence to the study of human malaria.¹

Among the early communications relative to the organisms now comprehended in this sporozoan order was one by Gaule in 1880 upon certain hematozoa of the frog and turtle, which he styled "Blutwürmchen," without appreciating their parasitic nature, which E. Ray Lankester was the first to note in 1882, calling the cytozoon of frogs' blood *Drepanidium ranarum*. Lankester had already recognized these worm-like bodies in frogs' blood as early as 1871. A systematic and fruitful study of this organism and of related forms in lizards, turtles, frogs, and birds was soon after made by Danilewsky, who established a separate species in the turtle, at the same time recognizing the affinities of these hemocytozoa with the sporozoa. With the hemosporidia of the cold-blooded animals we will not be concerned, only remarking that they differ from those of birds in the absence of pigment, and that, while they are the members first recognized in this order, their life history is by no means so well elucidated as that of more recently discovered forms.

Among the several communications dealing with the hemosporidia of birds, those of Labbé must be especially mentioned, since he carefully studied the organisms of avian blood and distinguished two forms of parasites which he regards as genera, one of these being designated *Halteridium*, and the other *Proteosoma*. But one species of each genus is thus far known. The developmental phases of both these organisms, a brief outline of which follows, have been quite well worked out. Several avian species serve as hosts for these hemocytozoa, and of those indigenous to the United States may be mentioned the crow, blackbird, English sparrow, song sparrow, and the great horned owl.

Proteosoma Grassi is the irregular form of hemocytozoon of birds, characterized by its indefinite shape and particularly by its position in one end of the nucleated red blood-cell of its host, where, on attaining a sufficient size, it gradually displaces the nucleus of the erythrocyte, pushes it to one pole of the corpuscle, and causes it to lie almost at right angles with the long axis. It first appears within the infected cell as a minute, colorless, refractive, nonameboid body, which rapidly increases in size, at the same time showing particles of black pigment in its parenchyma, derived from the hemoglobin of the erythrocyte. Attaining a size about equal to half that of the red blood-cell, the organism divides into a number of small round bodies, the segmentation being preceded by collection of the pigment

¹ The papers by MacCallum and Opie (*Jour. Exp. Med.*, iii., 1898) and one by Koch ("Ueber die Entwicklung der Malaria-parasiten," *Zeitschr. f. Hyg. u. Infektionskr.*, xxxii., 1899) may be consulted with profit by those interested in the various phases of comparative hemosporidian investigation.

into the center of the now spheric organism, and the appearance of peripheral indentations giving the intracorpuseular body somewhat the appearance of a roset. From five to twenty small bodies with a circular outline result from the segmentation of the mature parasite. The red blood-cell decolorizes, assumes a roundish shape, its nucleus swells and becomes more round, and finally the shell of the corpuscle that remains bursts, and the young proteosoma are set free. Appropriate staining by Romanowsky's method reveals a nuclear chromatin mass in the parent organisms and a division of this nuclear substance during the segmentation, furnishing each of the young forms with a particle of chromatin. The full life cycle of the young proteosoma has not been followed, but from analogy it is quite justifiable to look upon it as equivalent to the pyrogenetic cycle in human malaria and to conclude that these bodies are the agents of autoinfection, invading new red blood-cells to mature and segment as their ancestors did.

Besides the organisms that divide in the blood in the manner just described, this hematozoon appears in another form—that of somewhat larger nonsegmenting bodies with disseminated pigment. Celli and Sanfelice have considered these forms analogous to the crescents of human malaria, and Opie has observed them to become flagellated in birds' blood. From what we shall learn of the significance of the crescents in human malaria, it is highly probable that the larger nonsegmenting forms are of the same nature.

It is evident that the process of intracorpuseular segmentation and the production of new groups of young parasites insures their perpetuation in the individual host, but not beyond. This is an imperfect parasitic adaptation not in keeping with what occurs among parasitic forms generally. Some means for preventing extinction must exist, for it is well known that these hemosporidia persist and that they infest large numbers of the host species. This is about the aspect that the problem of hemosporidian parasitism presented, both as to the hemoctozoa of birds and those of human malaria, when new light came through studies on the proteosoma, which has illuminated the whole subject of etiology of hemoctozoan infections. For it was discovered that in the case of the proteosoma of sparrows, besides the evolutionary phase completed and repeated in the birds' blood, there was another completed in an insect—the gray mosquito (*Culex pipiens*). This second cycle, experimentally studied by Ross, marked the new era in hematozoic investigations which has already been so profitably turned to account in the case of human malaria. He found that proteosoma could be carried from an infected to a noninfected sparrow by the agency of the gray mosquito. By causing these insects to bite an infected bird, it was found that new pigmented cells made their appearance in the stomach- (mid-intestine) walls of the mosquito, and not in the stomachs of mosquitoes nourished on the blood of healthy birds. By studying from day to day the mosquitoes which were fed upon blood containing proteosoma, it was found that the peculiar pigmented cells became encysted, and that their substance ultimately divided into an enormous number of delicate filiform bodies which, on the rupture of the mother-cyst, became free and found their way into the body-cavity of the insect. Some of these filaments (germinal rods) made their way into the salivary poison-gland of the mosquito, which, if the insect was permitted to sting a healthy bird, infected the latter with proteosoma. The ordinary period for the fulfilment of this cycle in the mosquito, from the

sucking of the infected blood to the appearance of germinal rods in the salivary gland, was found to be eight days. These observations made by Ross have been fully confirmed, especially by Koch, who rigorously repeated them; and it is now thoroughly established that the significance of the phenomena witnessed here is the same as that in human malaria, even to the processes of a sexual nature that mark the inauguration of the second life cycle. Of these we shall learn more definitely in connection with *Halteridium* and the hematozoa of malaria in man.

Of the other principal hemosporidian parasite of birds (*Halteridium* of Labbé), we know less as regards the second evolutionary stage of existence. In the blood of infected birds it appears first as a small, round, clear body lying at the side of the nucleus of the red cell, soon ingesting pigment, and growing to fill one side of the corpuscle, without seriously displacing the nucleus; but elongating parallel with the long axis of the oval corpuscle, and curving its ends around the nucleus. After attaining its maximum size the halteridium becomes spheric, causes one side of the red cell to protrude and finally to burst, setting free the round pigmented parasite. Multiplication by a process of segmentation such as noted for proteosoma has not been seen in this parasite, although the double or multiple infection of the red cell in severe cases is likely to be mistaken for such a process. Having become free in the blood-plasma, the mature halteridium, after a short period of rest, shows a violent agitation of its pigment and suddenly projects several long filaments from its periphery, which whip about actively. This is the formation of flagella; the whips are flagella, and the phenomenon is identical with that witnessed in the hematozoa of human malaria. Soon these flagella become detached and swim about in the plasma. Up to this stage the process of flagella formation in halteridium had been often seen; but it remained for MacCallum to carry the observation a step further and to place the correct interpretation on this process, both as relates to the hemosporidia of birds and to those of mammals. Carefully studying the halteridium in crows' blood, MacCallum distinguished two types of mature halteridium: one larger, more granular, and quiescent, never becoming flagellated; the other smaller, hyaline, and more active, producing flagella. Watching these two forms in fresh preparations, he saw one of the flagella, set free from a hyaline form, advance to a granular form and penetrate it. This operation MacCallum correctly interpreted as an act of fecundation, considering the quiescent organism a female element, and the hyaline flagellated one a male; thus was the first actual observation made of sexual phenomena in the hematozoa. Applying the biologic nomenclature to these forms, the large quiescent organism is the female gamete or *macrogamete*, the more active smaller one the male gamete or the *microgametocyte*, while the flagellation is a process of spermatogenesis, the individual flagella being male copulative elements, spermatozoa, or *microgametes*; and the final act is one of fertilization. In the case of halteridium the product of this fecundation soon becomes an elongated, motile, worm-like organism, the so-called "vermiculus" of Danilewsky, the exact significance of which is unknown, although it is believed to be a resisting form of the parasite, by which it may enter upon its second life cycle.

Beyond the phenomena seen in the birds' blood, just briefly described, nothing is known of the life history of halteridium; that is to say, nothing is at present known of the mode by which the parasite is carried from bird

to bird, nor is it clear how auto-infection occurs. Evidently some intermediate carrier among the insects must be called upon, for the infection is extremely widespread among birds of certain species, as the crow, where every individual, from fledgling to adult, of a series examined from a given locality, has been found infested with halteridium.

Hemosporidia of Mammals.—Among the hematozoa positively recognized in a parasitic role in mammals, two are of particular interest to us, viz., (1) the hematozoon of Texas fever, and (2) the hematozoa of malaria.

The Hematozoon of Texas Fever.—This is a nonpigmented, endoglobular, actively ameboid organism discovered by Theobald Smith in cattle affected with Texas fever: a malady characterized by malarial manifestations, as fever, anemia, and hemoglobinuria, and often working great devastation to the cattle industry of southern countries, where the disease is endemic. The parasite is a pyriform organism, often appearing in the red blood-cells in pairs, hence the name *Apiosoma* (*Pyrosoma*) *bigenium*, applied to it by Smith. Free forms of the organism are also found in the blood-plasma, and Celli and Santori have distinguished two forms: a larger one with more pronounced ameboid movements, and a smaller one which moves *in toto* within the red blood-cell. The reproductive phenomena in this hemosporidium have not been thoroughly worked out, although Hunt claims to have found segmenting bodies in the capillaries of the endocardium.

The feature of most importance concerning this parasite, and one which had a marked influence in directing investigators into new fields of inquiry, was the discovery by Smith and Kilbourne of the intermediate host of Texas fever, the so-called cattle-tick (*Boophilus bovis*), a blood-sucking arachnidian insect infesting the skin of cattle. Exhaustive and apparently incontrovertible experimental studies have shown that this insect is the sole and active agent in transmitting Texas fever, and that the female tick, ingesting infected blood, permits the parasites to pass through her eggs to the larvæ, which, attaching themselves to healthy cattle, provoke the disease. Observations as to the phases presented by the parasite in the new host are entirely lacking; still, there is no disposition to dispute the correctness of Smith's conclusion. This most important pioneer work in the field of microparasitology was made between 1888 and 1892.

The Hematozoa of Malaria.¹—There is little reason to doubt that the specific parasite of the malarial fevers was seen by several observers before

¹ With the mass of information that has accumulated relative to malaria in its various phases, and more especially concerning the biology of the malarial parasites, no brief discourse, such as this must necessarily be, can do justice to the subject. It is therefore urged that more exhaustive treatises be consulted to fill in the numerous gaps, especially as to the details, that exist in this sketch. For this purpose the work by Marchiafava and Bignami, already referred to, should be studied. It presents an extensive bibliography, in which all the more important treatises and monographs on malaria are indicated. Information concerning the mosquitoes of the United States, which now becomes an important matter to the American student of malaria, may be obtained in the publications which the United States Department of Agriculture, Division of Entomology, is issuing to meet the demand. The technic of malaria investigation, and especially the Romanowsky staining method, which has given valuable information concerning the structural details of these and other protozoan parasites, are discussed in the current journals devoted to parasitology and pathology.

To the student of this fascinating branch of scientific investigation, it will be almost superfluous to point out again the desirability of personal, practical verification of at least some of the data already obtained: such, for instance, as might readily be done by studying the halteridium in the blood of the crow, and there witnessing the various phases of the parasite's behavior, including the wonderful phenomenon of fertilization.

Laveran definitely decided in 1880 the true nature of the peculiar bodies in the blood of persons suffering from malaria. This acute investigator was especially impressed with the parasitic character of these bodies when studying the flagellated organism, and in his early publications he differentiates several morphologic variations in his *Oscillaria malarie*, including the round, ovoid, crescentic, and flagellated, although undecided as to the intracorpuseular habitat of those peculiar to the red blood-cell. It was Richard who determined that the small nonpigmented bodies were contained in the substance of the erythrocytes, and not upon their surface, as Laveran believed. Among the pioneers in the field opened by Laveran's work, for several years unnoticed, Marchiafava and Celli are particularly prominent, since they extended in several important directions the knowledge already gained, and began the studies upon malarial lesions traceable to the havoc wrought by the parasites in the blood. Among the host of capable investigators who have since contributed to this important subject, individual mention is impossible in this place, although credit is especially merited by the Italian investigators who have so materially advanced this line of inquiry. In America, the workers in the Johns Hopkins Hospital, under the inspiration of Osler, have contributed liberally to our fund of information.

The exact zoologic position of the hematozoa of human malaria has not been indisputably settled, although most authorities now agree in including them among the class Sporozoa and order Hemosporidia, with the several hematozoa of lower animals. Labbé, however, divides these blood-parasites into two orders: (1) Hemosporidia, and (2) Gymnosporidia, placing the human malarial parasites in the latter order. It will scarcely be profitable to discuss other systems which have been proposed; but it is important to know that, as judged by their morphologic, reproductive, and pathogenic manifestations, the hematozoa (plasmodia) of malarial fevers in man can be sharply divided into at least three groups. Whether this division is to be regarded as of generic, specific, or only of varietal value is not determined; but for practical purposes and for didactic presentation it must be recognized. According to this classification, which has its origin in the clinical manifestations of the malarial fevers affecting man, we may distinguish: (a) the *Estivo-autumnal Hematozoa*, (b) the *Tertian Hematozoa*, and (c) the *Quartan Hematozoa*.

Even among these three groups, and particularly in that of the estivo-autumnal (summer-autumn) class, it is highly probable that several varieties of parasites are found; but for present purposes this grouping suffices. As has been said, it is founded primarily upon clinical manifestations exhibited by the patients suffering from malaria, which disease we now know to be directly and solely dependent upon the presence and multiplication of hematozoa in the red blood-cells; to these hematic parasites may be charged the intermittent fever and the anemia of malaria. At present we know that the cycle exhibited by the parasites in the human host is only one in its evolution, the others being completed in a second host—in this case an insect. In the human host, however, the parasite undergoes a complicated metamorphosis consisting in growth, reproduction, and renewed infection of the special cells which furnish its habitat—the red blood-corpuscles. To one of these metamorphoses, endoglobular multiplication, the fever of malaria is charged. In one group of malarial hematozoa this reproductive phase reaches its height in two days, marked by a fresh paroxysm of fever every third day;

these are *tertian* hematozoa. In another group the reproductive cycle is completed in three days, fever appearing on each fourth day: *quartan*

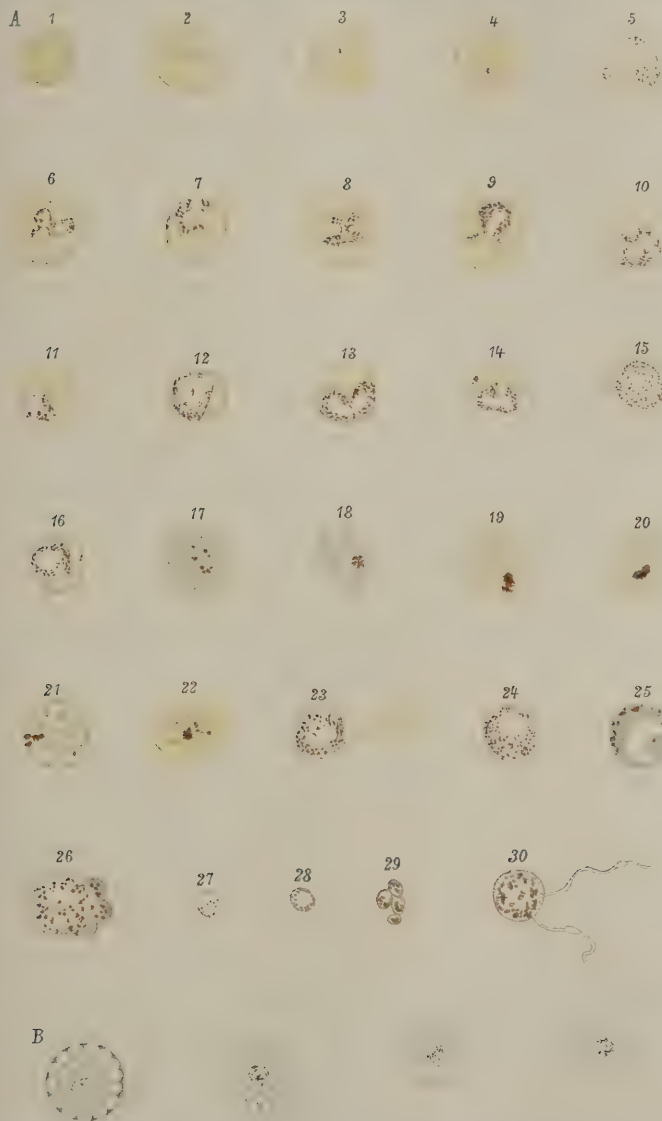


FIG. 99.—1-22, Developmental forms of the common tertian malarial parasite (Mannaberg) (Figs. 17 and 18 after Thayer and Hewetson); 23-29, hydropic, degenerated, disintegrating bodies; 30, flagellate body; B, schematic sporulation of the tertian parasite (after Golgi).

hematozoa. That such regular clinical paroxysms should occur, with comparative freedom from disease in the interval, as is the case in the regularly

remittent malarial fevers, it is evident that practically all of the vast number of parasites in the blood must reach the reproductive or "sporulation" stage simultaneously. This is precisely what occurs. In still another group of organisms, however, the reproductive cycle is irregular, infection by them occurring in the summer and autumn in temperate climates: these are the *estivo-autumnal hematozoa*. Two groups of a single kind of hematozoon may be present in a given patient, reaching the stage of multiplication at different periods; hence the modifications of the tertian and quartan remittent fevers familiar to clinicians.

Many of the morphologic and physiologic features of the various malarial hematozoa are quite similar, at least during the fever-producing or "pyretogenic" phase of their existence in man. They first appear in the red blood-cells of the host as small, clear, ameboid bodies, which, as they increase in size, procure their nourishment from the harboring cell, whereby they convert the hemoglobin into pigment, which finds its way into their substance. The amount and disposition of this pigment differ somewhat in the three types of hematozoa, and this is true for the motility of the pigment granules in the ameboid body. Thus in the regular tertian parasite, which has an obscure outline and is actively ameboid, the pigment is abundant, in fine granules diffused through the parasite, and usually shows motility. In the quartan parasite the pigment particles are longer and nonmotile, and the outline of the parasite (which is larger and more sluggish than the tertian) is clear. The estival parasites never attain the size of the other types; they tend more commonly to assume an annular or discoid form, and the fine granular pigment is arranged about the periphery of the organism and is rarely motile.

All three types of the malarial plasmodium, after attaining a certain size, multiply in the enclosing red blood-cell by a process of fission, an operation equivalent to sporulation, as already

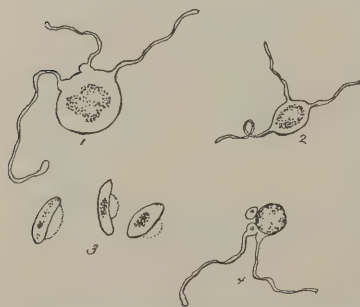


FIG. 100.—Crescentic and flagellated forms of *plasmodium malarie*: 1, flagellated form of tertian fever; 2, flagellated form of quartan fever; 3, crescents; and 4, flagellated form of estivo-autumnal fever (after Thayer and Hewetson).

mentioned in connection with sporozoa, the products of this fission being known here as *Gymnospores*. These fission products differ in the three types also. In the tertian parasite they number 15 to 20 and are smaller than those of the quartan, of which 6 to 12 are produced. Each quartan gymnospore shows a shining, highly refractive sphere, the *nucleus* or *nucleoliform* body, inconstant in the young tertian. In the estivo-autumnal type the spores are much smaller than in the tertian. During the fission of the mature endoglobular parasites, peculiar figures are produced, resulting from the radial direction of the

lines of segmentation; but these figures, which also differ somewhat in the three hematozoon varieties, agree in their general roset-like appearance, the larger ones of the quartan having been likened to a sunflower or a daisy with its expanded petals. At the completion of fission in these endoglobular parasites there remains a central portion, consisting principally of black pigment, the so-called "residuum of segmentation."

There is a further general resemblance between the bodies of the pyretogenic cycle in the three types of malarial parasites, in regard to the nucleus and the mode of nuclear division which takes place during fission. These characteristics have been only lately noted, and owe their recognition to the Romanowsky staining method, in which methylene-blue and eosin are mixed in definite proportions to produce a stain that colors the nuclear chromatin reddish or purple, and the cytoplasm varying shades of blue. After this procedure applied to properly fixed specimens of malarial blood, the mature intracorpusecular parasites have each a vesicular nucleus provided with one or more particles of chromatin. About the nucleus is the mass of cytoplasm with its black granules of pigment (melanin). The chromatin increases in amount as the parasite matures, and, at the moment of segmentation or fission, goes through a process of division roughly comparable with the karyokinesis of ordinary animal and vegetable cells, the isolated masses of chromatin being disposed in such a manner that the bodies resulting from segmentation of the parasite—gymnospores—form around the chromatin particles, each receiving its share.

So far our attention has been centered on only one phase of the life history of the malarial parasites: that passed exclusively in the body of the principal host—man. In the natural course of events the process just described repeats itself indefinitely, and is in reality a method of oft-recurring auto-infection, in which certain parasites mature, destroy a definite number of red blood-cells, reproduce themselves in multiple in the form of naked spores, these spores again invading new blood-corpusecles to repeat the series. As in the case of the proteosoma of birds, already discussed, no provision is made for the perpetuation of the malarial parasites—none for infection of other human beings; for it has long been known that malaria is not directly contagious. Here it was that all investigations came to a standstill until recently; and the significance of the irregular forms of malarial parasites, which are now to be described, was entirely conjectural.

Besides the forms of the pyretogenic cycle, each type of the malarial hematozoa exhibits others which, varying considerably in the different types, agree in that they do not multiply by fission in the host's blood and do not again infect blood-cells. For a long time these were called "sterile" forms, from their failure to multiply and also because they were finally seen to degenerate and disappear in the human blood. They are sterile in the organism of the principal host, and, failing to find the proper exit, they die; but this is not their natural destiny. In appearance, these sterile forms differ from those of the fever-producing cycle, and some of them are highly characteristic. They are, when spheric, generally larger on attaining their full size than the red blood-cells which harbored them, and larger than the forms multiplying by fission. They do not segment like the fission forms of auto-infection. Instead, when examined with the microscope in fresh preparations, some of them become flagellated by a process analogous to that already described for halteridium, the flagella finally becoming free and swimming in the blood-plasma. Other spheric forms never become flagellated. The exact morphologic significance of the various "sterile" forms of the tertian and quartan fevers has not been fully determined as yet; but in the case of the hematozoa of estivo-autumnal malaria, the sterile forms are well known during the greater part of their life history because of their characteristic semilunar or crescentic shape. Such *crescents*, first appearing in the

erythrocytes of blood-preparations from summer-autumn fever, then escaping to lie in the plasma, and finally contracting to assume an ovoid shape, either forming flagella or not, have long been known; and from their morphologic peculiarity and the impossibility of tracing their further development in man, they have always been objects of conjecture.

Sexual Phenomena.—We are now prepared to attempt an interpretation of some of the biologic characteristics of the malarial hematozoa. So far as the agents of auto-infection (of the pyretogenic cycle) are concerned, it is evident that they can only be regarded as asexual forms; that is to say, from the moment of entrance of the young ameba into the corpuscle to the time it reproduces its numerous progeny, which become free to repeat the cycle, no operation of a sexual import has been called into play. But the case is different in the sterile forms, certainly in the case of the crescents of estivo-autumnal malaria; for here MacCallum has seen an exact repetition of the process observed in halteridium, which was interpreted as an act of fertilization. He saw the crescents in the freshly removed blood from a case of human malaria quickly assume the ovoid shape that is peculiar to them when examined by the usual methods; some of the forms remained quiescent, others showed active pigmentary motion and suddenly projected flagella. The flagella soon became free and approached a quiescent form, into which one of them penetrated, the rest being refused admission. No particular change was noticed in the fertilized form. Here again we have evidence of a sexual process with the usual biologic significance: a process in which two forms participate—one male, the other female—the male cell or *microgametocyte* undergoing a process of spermatogenesis with resulting spermatozoa or *microgametes*, these microgametes fertilizing the female cell or *macrogamete*. When Romanowsky's stain is employed to study the forms concerned in these sexual phenomena, it is found that the nuclear chromatin of the parasites comports itself in a manner analogous to that seen in the sex-cells of higher animal forms. Thus far no maturation of the macrogamete has been observed; though, judging from what has recently been seen in the case of *Adela ovata*, it may be predicted that this will probably be found. However, during flagellation, the chromatin of the microgametocyte undergoes a reducing division, the result of which is to provide at least some of the flagella or microgametes with a long filament of chromatin.

So much for what is known of sex phenomena in the summer-autumn hematozoa, as actually witnessed. It has only recently been established that the tertian and quartan parasites go through a process similar to that just mentioned. Flagellation has been repeatedly seen in both these forms, and Romanowsky's stain determines that here also the chromatin of the parent cell is disposed so as to endow the flagella with nuclear material.

The Intermediate Host.—How is malaria carried from person to person? What provision is made for the perpetuation of these highly evolved parasitic organisms, which, in the case of the human host alone, have a life cycle adapted only to the particular individual in whose blood they thrive? Experiment has thrown some light, in that it was found possible to inoculate healthy men by subcutaneous or intravenous injections of blood containing malarial organisms, so as to produce the fever characteristic of the particular type of hematozoa present in the infected man. All other attempts to cause infection through air, water, and by contagion were fruitless; and,

of course, the method of direct inoculation is not Nature's method. It was at this stage of the problem that Smith's observation on the role of the cattle-tick in Texas fever, and of Ross on the gray mosquito in bird malaria, directed the attention of students of human malaria into similar channels, with the result that to-day we have overwhelming evidence to show that *the mosquito is the chief agent, if not the only one, in transmitting malaria from one person to another*. Of the interesting and elaborate investigations—many of which are still in progress—which led to this result, it is impossible here to speak in detail; but the results are widely accepted as unquestionably authoritative. And we may now speak with confidence of the other stage or cycle in the evolution of the malarial parasites: that passed in their intermediate host, the mosquito. Recorded observations have furnished many details with reference to the estivo-autumnal hematozoon, and the same phenomena have been observed, with certain minor modifications, in the tertian and quartan parasites. We shall consider only those best known and least open to modification, relating to the estivo-autumnal parasite.

The second cycle in the life history of the estivo-autumnal hematozoon is in a general way as follows: A mosquito of the proper species and sex stings a human being whose blood contains malarial crescents—these being the so-called sterile forms not capable of producing auto-infection, or, in other words, incapable of asexual reproduction—abstracting some of the blood, which finds its way into the stomach (mid-intestine) of the mosquito. Here the crescents are set free and become ovoid; some flagellate; others do not, but, remaining quiescent, are fertilized by the flagella.¹ Here again we have the biologic equivalents—the *microgametocyte* producing the *microgametes*, which in turn fertilize the *macrogamete*; but, contrary to what is observed in artificial condition, the life history of the fertilized or gamic cell may now be followed. What happens here is much the same as noted in protosoma when ingested by the gray mosquito. The fecundated or gamic cell traverses the epithelium of the mid-intestine, to find its way between the muscle-fibers or in the adipose tissue adjoining the muscular layer; here it comes to rest, and, for a period estimated at about eight days for the hematozoon of estivo-autumnal malaria, under favorable conditions of temperature, undergoes a striking transformation. The pigmented body increases rapidly in size, becomes enveloped in a capsule, and projects more

¹ At this writing, the actual phenomenon of fertilization has not been witnessed in the stomach of the malarial mosquitoes (genus *Anopheles*); but there is every reason for believing that this is where it takes place. It may seem contradictory to find that flagellation and fertilization can take place in freshly removed malarial blood; that is, *in vitro*, as MacCallum and others have seen in the case of halteridium and the estivo-autumnal parasite; from which some have too hastily concluded that the same operation takes place in the circulating blood of the principal host, although it has long been known that flagellated organisms only appear in extravasated blood, and not until some little time has elapsed. In all probability no spermatogenesis and no fertilization of hematozoan forms predestined for sexual purposes take place in the circulating blood of the principal host; but in the operation of removing the blood for microscopic examination some physical change is induced (some restraining influence abolished?), permitting the extrusion of the flagella, which then go on to perform their function of fertilization. Something of the same kind, but probably more perfectly adapted to the purpose, must happen when the blood is sucked into the proboscis and stomach of the mosquito. Probably because of the less perfect conditions afforded by our laboratory methods of examination, the act of flagellation is somewhat abnormal, accounting for the irregular and often degenerative phenomena here witnessed. If it has not already been done, a method of examination in which the sucking apparatus of the mosquito, or its juices (like those of the mid-intestine), are employed as a medium, will perhaps be found to yield results more like those taking place naturally.

and more into the celoma or body-cavity (pleuroperitoneal cavity in higher animals). Its protoplasm becomes striated and finally breaks up into innumerable filaments, each of which is provided with a speck of chromatin from the nucleus of the mother-cell (*sporocyst*). The products of this much-repeated nuclear and cellular division, the nucleated filaments, are embryonic hematozoa—that is, *sporozoites*. They are slender filaments, usually slightly curved, in the center of which are a few particles of chromatin. The capsule of the sporocyst breaks, and the sporozoites swarm into the body-cavity of the mosquito, many of them finding their way to the tubules, acini, or lumens of the salivary poison-gland of the insect, from which point of

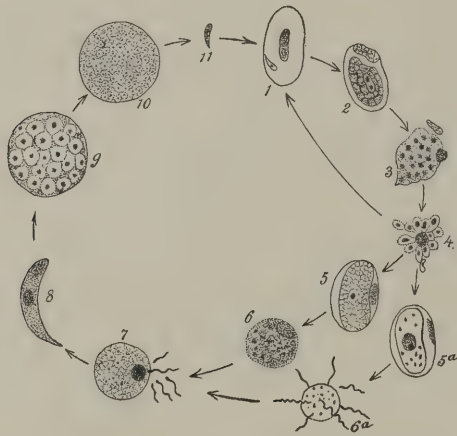


FIG. 101.—Developmental cycle of proteosoma (diagrammatic) (after Schaudinn): 1. Sporozoite (merozoite), after penetration into a red corpuscle. 2. Adult schizont. 3. Nuclear multiplication preparatory to schizogony (asexual propagation). 4. Formation of merozoites (schizogony). 5 and 5a. Immature sexual elements (5, macrogamete; 5a, microgametocyte). 6 and 6a. Mature sexual individuals (6, macrogamete after expulsion of the karyosome; 6a, microgametocyte in stage of microgamete-formation). 7. Copulation. 8. Ookinete—the elongated motile body resulting from copulation. 9. Formation of sporoblasts in the oocyst. 10. Sporozoite-formation. 11. Sporozoite.

vantage they are readily inoculated into the human being with the secretion of the gland, when the mosquito again stings. Fig. 101, from Schaudinn, gives a good representation of the present views concerning the developmental cycle of proteosoma, and also represents that of the *Plasmodium malariae*.

Malarial Mosquitoes and the Mode of Infection.—The process sketched above has been fully verified by experiments carried on in the laboratory and at the bedside. Estivo-autumnal malaria has been induced in human beings by causing them to be bitten by malarial mosquitoes which had sucked from infected patients the blood containing the *gametes* or crescents, and, after the interval previously determined as requisite for the dissemination of the sporozoites, used as agents of infection. These experiments on man, obviously few in number, are only the repetition of those successfully carried out by observers in numerous instances with the proteosoma of birds.

In the course of these experiments, however, it has been determined that only certain kinds of mosquitoes serve as the intermediary host for the plas-

modia of human malaria; in fact, at present only members of the genus *Anopheles* have been found to act as agents of infection. Probably all species of this genus are capable of transmitting malaria, although actual observations have thus far been made in Europe on only three species: *A. claviger* (*maculipennis*) [equivalent to *A. quadrimaculata* of the United States], *A. bifurcatus*, and *A. pictus*. None of the more common mosquito genus *Culex* has been found to harbor the malarial organism of man. Zoologic study upon these malarial mosquitoes has determined that only the females obtain nourishment by sucking human blood—that is to say, only the females of anopheles carry malaria; and the appearance of malaria in certain districts has been found to correspond perfectly with the predatory habits of these mosquitoes. Nothing positive has been discovered as to the possibility of the malarial sporozoites finding their way into the eggs of anopheles, and from here to the larvæ, though such a process is not an improbability. The data concerning the epidemiology of malaria, as now explained by the distribution and life habits of the malarial mosquitoes, cannot here be detailed; but before dismissing this important new phase of parasitologic investigation, we must refer to the positive results in the crucial tests of the malarial mosquito theory now in progress in the deadly Roman Campagna, where two observers are living in perfect health in the midst of

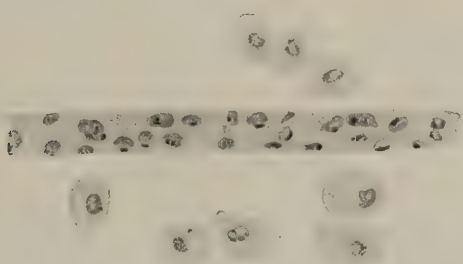


FIG. 102.—Brain-capillary with pigmented tertian parasites (after Celli) (Mannaberg).

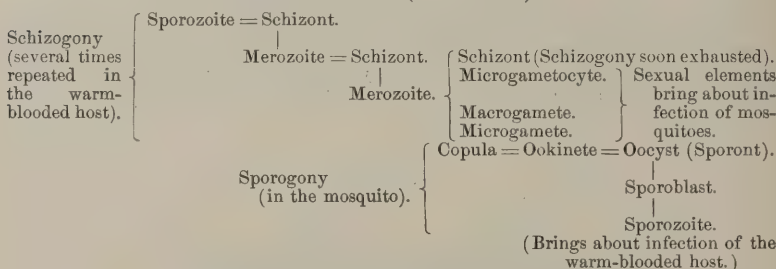
this notoriously malarious swamp, with only the mechanic protection against the ravages of mosquitoes afforded by a mosquito-proof dwelling.

Morbid Effects.—The chief effect of simple malarial infection is the destruction of red blood-cells and the setting free of blood-pigment, which is taken up by the cells of certain organs, especially the spleen. The sterile parasitic forms, or gametes, which do not find exit, also disintegrate, not infrequently falling a prey to phagocytes, particularly those of leukocytic origin. The task of ridding the body of pigment and of defunct parasites falls to the phagocytes; and this is why phagocytosis, both by the leukocytes and fixed-tissue cells, is so prominent a phenomenon in malarial infections.

In the so-called pernicious agues and in the cachexia of chronic malaria, more pronounced gross and microscopic lesions are found. The spleen is enlarged, sometimes soft and pultaceous, due to intense engorgement of the blood-vessels of the pulp; again firm, especially in cases where the reticulum is increased in amount and the vessels of the pulp dilated. A diffuse deposit of pigment is evident. The liver also is swollen, and microscopically shows diffuse pigment and a plugging of many of the finer blood-vessels with

phagocytes. Thrombosis may be the result, and may, according to Barker, bring about the focal necroses at times seen in the liver. The brain may show either microscopic or macroscopic pigmentation; and in the cerebral capillaries the blood is seen to be extensively infected with parasites and to harbor numerous phagocytes. These vessels are often occluded by the infected red cells and phagocytes, producing a deleterious effect on the vessel-wall, by which the cerebral focal hemorrhages of pernicious malaria are produced. Infection of the blood in the vessels of the gastric and intestinal mucosa is also observed at times; and the kidneys frequently suffer parenchymatous degeneration. In pernicious hemoglobinuria this alteration of the kidney is encountered, and the liver also may show diffuse parenchymatous degeneration, its biliary canals being extensively injected with inspissated bile.

SCHEME SHOWING CYCLE OF DEVELOPMENT OF PLASMODIUM IN TABULAR FORM (from Lühe).



PARASITIC INFUSORIA.

Among the free-living forms, the protozoan class Infusoria includes a large number of representatives. Its parasitic members are not so numerous and belong chiefly to the flagellate group. On morphologic grounds the parasitic infusoria may be divided into the subclasses *Flagellata* and *Ciliata*.

Flagellata generally have a pyriform shape, both ends being acuminate; the end put forward in progression is more pointed and is continued into one or more long appendages or flagella. Several organisms belonging in this category are also provided with a so-called undulatory membrane, a peculiar structure extending along the body-wall and showing a rhythmic wave-like motion. This structure, the nature of which was indefinitely understood, is revealed as a red filament in certain flagellata stained by the Romanowsky method, and is continuous with the flagellum, being anchored in the posterior portion of the organism by a round red body. Treated by this method, these flagellata also exhibit a well-defined oval nucleus situated in the parenchyma, usually near the anterior end.

Reproduction takes place by direct binary fission of the mature flagellata. A process of conjugation has also been witnessed, and a difference in the conjugating bodies has suggested a distinction into male and female individuals. In certain species an asexual mode of reproduction has been observed (in *Trypanosoma* of the rat), and here the division of the nucleus, the formation of new flagella from the spheric body anchoring the maternal one, and the division of the cytoplasm have been noted. In some cases a large

plasmodial mass, with numerous nuclei in various stages of indirect division, can be seen before the flagellata separate and leave the colony.

Parasitic flagellata have been encountered in the body-cavities principally, although one genus infests the blood of vertebrate animals. Although their classification is imperfect, several genera have so far been distinguished.

The genus **Plagiomonas** of Grassi, or **Cystomonas** of Blanchard, is characterized by two anterior flagella and a long, tapering, flagella-like posterior end. Here one human parasitic species is included, *Plagiomonas urinaria*, found by K  nstler in the freshly passed urine of a patient suffering with chronic purulent cystitis.

The genus **Trichomonas** (Donn  ) includes flagellata with three or four flagella, often united, and with an undulatory membrane. The posterior portion is decidedly acuminate, but not prolonged into flagella. It includes several parasitic species, some having long been known. One of these, *Trichomonas vaginalis* (Fig. 103), is variable in shape, spindle-formed, or irregular. Its anterior end is generally provided with four flagella, united at their base. A spiral undulatory membrane passes over its body. Near the base of the flagella the organism has a mouth and short esophageal pouch, and in its parenchyma a nucleus is situated. As the name indicates, the habitat of this organism is the vaginal secretions; and since it appears in apparently healthy women, it is questionable whether it can excite the vaginitis which has sometimes been ascribed to it. In a case of cystitis in which no other exciting factor could be determined, Dock found an organism apparently identical with *T. vaginalis*, and he thought the flagellate to be pathogenic. *Trichomonas* (*Cercomonas*) *hominis* resembles the foregoing organism, except that its undulatory membrane is hardly visible and it has several vacuoles, none of them contractile. It has been repeatedly encountered in the stools of human beings under a variety of conditions, as in



FIG. 103.—*Trichomonas vaginalis* (after K  lliker and Scanlon).



FIG. 104.—*Trichomonas intestinalis* (after Zenker).

cholera, typhoid fever, chronic enteritis, and acute or subacute diarrheal affections. Epstein records the presence of this parasite in twenty-six children suffering with diarrhea. The pathologic significance of the organism is, however, not known. Grassi claimed negative results in attempting to infect dogs with feces containing the *Trichomonas*. But Epstein is positive that in the case of six children in one family, who simultaneously developed diarrhea, the trichomonads, present in their stools and absent in a nursing infant of the same family, were the etiologic agents. On the other hand, Schuberg and others have found flagellata resembling this species, and

also amebæ, in healthy persons after the exhibition of saline cathartics; so that in all probability these protozoa usually exist in the intestines of man in a state of commensalism. Quinke has described a number of cases, some fatal, of so-called *protozoan enteritis*, in which both flagellate and non-flagellate organisms were found. He claims to have definitely identified, as provocative of diarrheal and sometimes dysenteric symptoms, *Trichomonas intestinalis* (Fig. 104), *Cercomonas hominis*, *Megastoma entericum*, *Coccidia*, *Balantidium coli*, as well as *Amœba coli*.

Another flagellate genus is **Lamblia** of Blanchard, the principal parasitic species of which is *Lamblia intestinalis* (*Megastoma entericum* of Grassi). This organism—which, like the other flagellata, is pyriform—is distinguished by the possession of an adhesion-apparatus in the form of a concavity near its larger end, provided with a contractile elevated ridge or lip, and by the presence of four pairs of flagella, two pairs of which arise from the lowermost or posterior portion of the adhesion-excavation, one from its uppermost or anterior portion, and one from the acuminate posterior extremity of the



FIG. 105.—Infusoria found in the stools in protozoan enteritis (after Salomon).

organism. The organism is endowed with a dense cuticle, the protoplasm is finely granular, and a dumbbell-shaped nucleus lies at the bottom of the excavation. By virtue of its adhesion-apparatus, the organism attaches itself to the epithelial cells of the intestine. It has been found in various diarrheal affections, but its pathogenic effect is questionable; from its frequent presence in the stools of healthy individuals, it is generally regarded as a harmless messmate. Grassi has described an encysted form of the organism, the oval cysts being found in the stools.

Flagellata have also been found in the sputum in cases of pulmonary gangrene, and in the gangrenous pulmonary parenchyma at autopsy. These observations have been several times confirmed from different sources, and the organisms were also found in the pleural exudate in a case of pulmonary gangrene, and once in pleural effusion where no such disease of the lungs existed.

Another group of flagellata, sometimes classed as a separate genus or family, is **Trypanosoma**, comprising organisms of an elongated spindle-

shaped outline, with a single flagellum and a well-defined active undulatory membrane. This is the class of flagellata in which the Romanowsky stain shows the continuity of the flagellum and the undulatory membrane referred to above. The type of this group is *Herpetomonas Lewisii*, discovered in the blood of the rat by Osler, and recently made the subject of interesting studies by Rabinowitsch and Kempner, who have concluded that the active agent in carrying this organism from rat to rat is a flea infesting these rodents. Direct infection by means of these fleas could not be produced in the laboratory; but, by causing these insects to ingest the blood of a rat infected with this trypanosoma, other rats could be infected by intraperitoneal injections of an emulsion made of the crushed fleas in sterile fluids.

Trypanosoma sanguinis is still another representative of this class of flagellata, appearing in the blood of amphibia, fishes, and birds, although apparently of no pathogenic significance.

Somewhat in keeping with the results obtained in the case of the trypanosoma of rats are the recent investigations upon two peculiar diseases of horses, mules, and camels in India, known as the *Surra disease*, and *Nagana* or the *Tsetse-fly disease*, which also affects cattle and dogs. Evans discovered a flagellate organism in the blood of animals affected with Surra disease, and Bruce found one in the tsetse-fly disease which he thought to be the specific causative agent. Koch confirmed these conclusions and believes that the two affections, as well as the flagellata, are identical. Injections of infected blood suffice to transfer nagana, and Bruce believes that the tsetse fly is the intermediate carrier of the infecting flagellata, a view concurred in by Plimmer and Rose Bradford.

Among the **Ciliata**, which include a number of highly differentiated protozoan organisms familiar to zoologists, two representatives only need be mentioned: *Balan-tidium coli* (Fig. 106) and *Vorticella*. The first organism, which has a close morphologic resemblance to the familiar slipper animalcule of standing water, has often been encountered in normal human feces, and especially in that of diarrheal disorders. Its pathogenic action is questionable. *Vorticella*, illustrated by the bell animalcule of fresh water, has been found by Lindner in the human being under a variety of conditions, as in the stools of a typhoid patient, in the urine, in the nasal secretion, and in an eczema-like disease of the skin. It is well known that this organism, generally anchored by a contractile stalk, can free itself and swim about in fluids; and in this state it might find access to the human body. Lindner's observations, however, need confirmation, since they assign much importance to these vorticellæ as pathogenic organisms.



FIG. 106.—*Balan-tidium coli* (after Malmsten).

ANIMAL PARASITES.

PARASITISM IN GENERAL.

THE dominant condition in parasitism, says Davaine, is "the subordination of one individual to another individual which is never of its own family." The condition of parasitism has a wide distribution, both in the vegetable and animal kingdoms; and man, in common with other representatives of the latter, harbors many forms of parasitic animal life.

Most parasites require a change of abode before arriving at maturity, therefore the animal which shelters the parasite during its immature existence is called the "intermediate" host, as distinguished from the "definitive" host in which development is completed. A few species require no intermediate host. Leuckart divides parasites into "stationary," those whose stay in the one host may be for their life, and "periodic," those whose stay is only a part of their cycle of life. Another division frequently used is that into external (ectoparasites or ectozoa), and internal (entoparasites or entozoa). The former class is made up principally of insects, the latter of worms.

The changes produced in the host by the parasite vary greatly in their consequences. In the case of tapeworms, for instance, no great amount of nourishment is abstracted from the body. Heller states that the average weight of eight specimens of *Tænia solium* was 10 grams, the maximum 19.9, and the minimum 5.1. The average weight of *T. saginata* was 42 grams, the maximum 64, the minimum 31. Since a tapeworm requires at least eight weeks to become mature, the loss could not exceed 64 grams, which would be quite insignificant. It is entirely different with the species living on the blood, for here the continued drain entails serious and even fatal consequences. However, even in these, it is only their presence in large numbers that renders them formidable (*Ankylostoma*). It is needless to say that, if parasitism in general were very dangerous, the condition would ultimately cease, owing to the death of all the hosts.

Some worms, especially the Nematodes, are intensely irritating when handled. Miram, while studying the round worm, was attacked by sneezing, swelling of the lacrimal passages, itching and swelling of the fingers. Cobbold

Berenger-Feraud : *Leçons cliniques sur les Ténias de l'Homme*, Paris, 1894.

Blanchard, Raphaël : *Traité de Zoologie Médicale*, Paris, tome i., 1889, tome ii., 1890; article "Parasites Animaux," in *Traité de Pathologie Generale* (Bouchard), tome ii., p. 649, Paris, 1896.

Braun, Max : *Die Thierischen Parasiten des Menschen*, 2te Auflage, Wurzburg, 1895.

Davaine, C., et Laboulbene, H.: Article "Parasites, Parasitisme," in *Dict. Encyclopédique des Sciences Médicales*, 2me series, vol. xxi., p. 66.

Heller, Arnold : Article "Intestinal Parasites," in Ziemssen's *Handbook*, vol. vii., p. 669, New York, 1876.

Leuckart, R.: *Die menschlichen Parasiten*, vol. i. Translated by W. E. Hoyle, Philadelphia, 1886.

Manson, Patrick : Article "Worms," in Allbutt's *System of Medicine*, vol. iii., p. 1006, New York, 1897.

and Bastian have noticed the same effects even in alcoholic specimens, the latter having catarrhal symptoms for six weeks. Lussana and other authors believe the pathologic symptoms produced by *Ankylostoma* are due to some poison given off from the worms themselves. The broad tapeworm (*Bothriocephalus*) is another species which seems to secrete some poisonous material.

Concerning the effects on the parasite, it may be said that many of the organs necessary for its life in a free state have degenerated or entirely disappeared on account of the change in environment. The reproductive organs, on the contrary, have become more prominent, and the body of many parasites is chiefly composed of these organs. The ova are produced in almost incredible quantities, probably owing to the vicissitudes to which they are liable. Leuckart points out that during an average life of a tapeworm it will produce about 1500 segments, each containing some 53,000 ova, or a total of say 85,000,000. Now, since the number of tapeworms remains about the same, only one of all these millions reaches maturity. The probability against a tapeworm egg ever becoming a mature animal is as 85,000,000 to 1.

The adult parasites are usually found in those cavities communicating with the exterior; the immature forms are scattered through the body and do not exhibit such marked preferences for certain locations as do the adults.

Bunge kept worms in a medium deprived of oxygen, in which they remained alive from four to seven days, exhibiting great activity. He suggests that parasitic worms have descended from anaerobic free-living forms, whose ancestors again were aerobic. As corroborating this theory, Bunge points out that nematode ova will not develop without oxygen; hence the young worms are not parasitic at first, but as a rule live free.

Individuals at all ages are liable to be attacked by internal parasites. Some species are found chiefly in children and young persons, others are met with at all periods of life to extreme old age. The female sex is more exposed to helminthiasis on account of active participation in culinary affairs, about 60 or 70 per cent. to 30 or 35 per cent. of males. Occupation also has considerable influence. (Of 173 patients of Wawruch, 39 were cooks, 26 servant-girls, and 13 innkeepers or butchers.) The season of the year is of some importance. The tapeworms seem more abundant in the winter on account of the great use of a flesh diet then; *Oxyurus* in the spring, *Ascaris* in the spring and fall, etc. Persons living in the country are more exposed to parasites than town dwellers, both on account of the more favorable opportunities for infection and the greater use of unfiltered water (57.31 per cent. country children, 16.66 per cent. city children, Langer).

In man, as in other animals, the vast majority of parasites belong to the subkingdoms Vermes and Arthropoda.

VERMES (Worms).

The parasitic worms belong to two classes—the flat worms and the round worms.

Plathelminthes.—Plathelminthes or flat worms have a flattened body, with the organs embedded in the parenchyma; there is no body-cavity. Of the three families comprising them, only two are parasitic.

Trematoda (Flukes).—The Trematodes or Flukes are worms with a soft, flattened body, not segmented, and ovate or lanceolate in shape. The body is smooth or covered with small spines directed backward, and provided with one or more suckers, of which the posterior one only is used for adhering to the body of the host (Fig. 107). Most of the species are hermaphrodite; the ova develop into ciliated free-swimming larvæ which require one or more intermediate hosts before arriving at maturity in the final host. It is an interesting fact that species of Trematoda which are capable of living in the stomach of one host are, as a rule, quickly digested when placed in the stomach of a strange host. This has led several observers, notably Max Braun, to conclude that the cutaneous secretion only protects each species against the juices of its proper host.



FIG. 107.—*Fasciola hepatica*, natural size, viewed from ventral surface.

Fasciola hepatica (*Distoma hepaticum*), the liver fluke, is a frequent parasite in sheep and cattle, occupying, as its name indicates, the bile-passages. In man it is found occasionally in the gall-bladder, bile-ducts, blood-vessels, and subcutaneous tissues; about two dozen cases have been reported to the present time (Fig. 107). This species is from 15 to 35 mm. in length and from 4 to 15 mm. in width, white, with body pointed at each end, and two suckers—the oral, into which the pharynx opens, and a larger one close behind on the ventral surface. The external surface is covered with spines. The eggs are yellowish brown, oval, quite large, measuring 0.13 to 0.15 by 0.07 to 0.09 mm., and furnished with a lid.



FIG. 108.—Papillary thickening of the mucous membrane of the bladder, showing distoma eggs *in situ* (Mosler and Feiper).

In sheep this worm gives rise to the "rot," which is exceedingly fatal in some years. In man the bile-passages may be enlarged, their walls thickened or obstructed. The liver may also be enlarged, and there may be hepatic pain, jaundice, vomiting, diarrhea, and ascites. In some cases no pathologic effects seem to have ensued. If only one parasite is present, its location may have some influence—*e. g.*, if it is located in the common bile-duct or the hepatic duct. Owing to the usual location of the worm in the bile-passages, the only means of diagnosis is the microscopic examination of the feces for eggs. The egg resembles that of *Bothriocephalus latus* (q. v.), from which it may be distinguished by its much larger size. Infection

occurs through ingestion of water containing the embryos or of food-plants containing the encysted larvæ.

Dicrocoelium lanceolatum (*Distoma lanceolatum*), the small liver fluke, is nearly as widespread in sheep and cattle as the former and is frequently associated with it. The body is 8 to 10 mm. in length by 2 to 2.5 mm. in width, white, thin, and broader posteriorly. The two suckers are farther

apart than in the preceding, and the genital pore is found between them. The eggs are black, 0.04 to 0.045 by 0.022 to 0.08 mm., and are also provided with a lid. It has been discovered five times in man, in one case associated with the former species. The lesions caused are the same, but it appears to inflict less damage on account of its much smaller size.

Opisthorchis felineus (*Distomum sibiricum*) is found in the bile-passages of the domestic cat. This fluke is 10 to 13 mm. in length by 2 to 2.5 mm. in breadth; the eggs are oval, 0.026 to 0.030 by 0.010 to 0.015 mm. It has been found in the cat in various parts of Europe, and once in this country by Ward. In parts of Siberia it is one of the commonest parasites of the liver, about Tomsk occurring in 6.45 per cent. of the necropsies (Winogradoff). According to this author, the lesions it may cause are atrophy of the liver, icterus, ascites, and less frequently hypertrophy of the liver and suppurative cholangitis. Several hundred individuals are sometimes found in a single cadaver.

Opisthorchis conjunctus (*Distoma conjunctum*) is 10 to 12 mm. in length by 2.5 mm. in width; the anterior sucker is larger than the posterior and in close proximity to it. The surface is covered with small spines, by which it may be distinguished from the next species. The eggs are oval, 0.034 by 0.020 mm., and furnished with a lid. It has twice been found in man in India. Both cases presented thickening and dilatation of the bile-passages, in which the distomes were very abundant.

Opisthorchis sinensis (*Distoma sinense*) is 10 to 15 mm. in length by 2 to 4 mm. in width, with a narrow, translucent, colorless or slightly reddish body and a smooth surface; the posterior sucker is smaller and situated far back. The eggs are oval, blackish, 0.028 to 0.030 by 0.016 to 0.017 mm., and are provided with a lid. This species resembles *D. lanceolatum* and *O. conjunctus*. In *O. sinensis* the posterior sucker is smaller, in *D. lanceolatum* the anterior is the smaller. In *O. sinensis* the cuticle is smooth, and in *O. conjunctus* spiny. It has been found in India, Tonkin, China, Formosa, Corea, Japan, and once in New York City. It has not yet been found in Europeans. In low-lying parts of Japan, according to Bälz, fully 20 per cent. of the population is affected. The liver and spleen become enlarged, there are chronic diarrhea, recurrent jaundice, and later ascites. Nutrition is not affected till late, for Bälz saw patients working in the fields who had been suffering for six years.

Opisthorchis Buski (*Distoma crassum*), the largest fluke known to attack man, is 4 to 8.5 cm. in length by 1.7 to 2 cm. in width; the body is elongate, narrower in front, very thick and smooth; the suckers are close together, the posterior being the larger. The eggs are 0.125 by 0.075 mm., with a lid. It inhabits the small intestine, and has been found in India, Assam, Straits Settlements, China, and in an East Indian coolie in British Guiana. In parts of India it is very frequent, and was found by Dobson in 1 per cent. of the coolies. It produces symptoms of intestinal irritation, indigestion, diarrhea, but no dysentery, although clots of blood may be in the stools.

Mesogonimus heterophyes (*Distoma heterophyes*) is 1.5 to 2 mm. in length by 0.7 to 1 mm. in width. The body is an elongate oval, with the posterior end rounded off, reddish in color from the contained eggs, and the front half is covered with spines; the posterior sucker is unusually long and situated about the middle of the body. The eggs are 0.025 by 0.015 mm., and reddish in color. It is found free by hundreds in the small intestine;

but, unlike the species mentioned hitherto, its intestine contains no blood and it is presumed to be harmless. Up to the present time it has been met with only in Cairo, Egypt.

Mesogonimus Westermanni (*Distoma Ringeri*, *D. pulmonale*) is the cause of "endemic hemoptysis." It is 10 to 16 mm. in length by 5 to 8 mm. in width, reddish brown, covered with spines, and in transverse section is nearly circular. The eggs are 0.08 by 0.05 mm., reddish brown, with a thin shell and lid. It is extremely frequent in Formosa, at least 15 per cent. of the population being affected (Manson), and is equally frequent in Japan, where Bälz found over 100 cases from all parts of the country; it also occurs in Corea. In this country it has been found by Ward¹ in a cat at Ann Arbor, Mich., and by Kellicott in a dog at Columbus, Ohio. The usual site is the lung, the parasite being found in cavities in the periphery of the organ, which communicate with the bronchi by small openings and contain mucopurulent fluid more or less tinged with blood, containing flukes, eggs, and Charcot-Leyden crystals. It is also found in the liver and peritoneum, and not infrequently emboli of the ova become lodged in the brain, where they give rise to cortical epilepsy. The patients have a constant cough, with expectoration of sputum colored like that in pneumonia, due to the numerous eggs. The cavities open into the blood-vessels, from time to time causing attacks of hemoptysis.

Schistosomum hæmatobium (*Bilharzia hæmatobia*, *Distoma hæmatobium*).

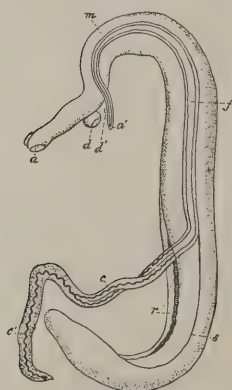


FIG. 109.—Male and female *Schistosomum hæmatobium* in the act of copulation. The male (*m*) encloses in its ventral groove (*r*) a female (*f*), whose two extremities are free and pendent; *a*, cupped mouth of the male; *a'*, cupped mouth of the female; *c*, intestinal branches; *c'*, single cul-de-sac proceeding from their junction in the posterior portion; *d*, abdominal cup of the male; *d'*, abdominal cup of the female; *s*, base of canal (after Bilharz).

—In this species, the cause of "Egyptian hematuria" or bilharziosis, the sexes are separate (Fig. 109). The male is 11 to 14 mm. in length by 1 mm. in width, whitish, the sides of the body folded over to form the gynecophoric canal in which part of the female is contained *in coitu*. The female is 15 to 20 mm. in length, very thin and darker in color. The eggs are elongated, 0.12 by 0.04 mm., with a spine either at one pole or placed laterally. It is found in Egypt, Abyssinia, Arabia, Mesopotamia, and South Africa; occasionally elsewhere, *e. g.*, in a donkey-boy from Egypt at the World's Fair in Chicago (Hillmantel).² It is very frequent in Egypt, and was found by Griesinger 117 times in 363 necropsies, and by Son-sino 30 times in 54 necropsies. It attacks either the genito-urinary system, producing vesical symptoms, or the rectum, causing dysenteric symptoms. The fluke is found in the portal vein, and its branches in large numbers (as many as 300 by Kartulis) in the renal veins and in the venous plexuses about the bladder and rectum (uterine, vesical, and hemorrhoidal). Its presence causes blocking of the vessels by ova, and leads to catarrhal inflammation with small hemorrhages in

the mucous membrane of the bladder and ureter. In cases of long standing there is proliferation of the connective tissue, and the surface of the mucous

¹ Ward, *Med. News*, p. 236, March 2, 1895.

² *Chicago Med. Rec.*, p. 230, Oct., 1893.

membrane is studded with small papillæ made up of proliferated cells encrusted with urinary salts (Fig. 108). The eggs are found in the tissues and the mucus covering the surface. Similar changes take place in the rectum when it is involved, and polypoid growths occasionally develop. Primary infection of the vagina is rare, but when it occurs the same changes are found. The principal symptom of bilharziosis is hematuria, varying in amount from a few drops to a large quantity. The characteristic ova are found free or else entangled in clots of blood and mucus in the urine when it is allowed to settle. Lortet estimates that from 3000 to 4000 eggs are voided daily with the urine.

Amphistomum hominis is 5 to 8 mm. in length by 3 to 4 mm. in width; the posterior sucker is very large and much wider than the remainder of the animal; the genital pore is situated between it and the oral sucker. It is found in India and Assam, occurring by the hundreds in the large intestine (cecum, appendix, and ascending colon). It was originally found in two cases of Asiatic cholera, and its importance is problematic.

Cestoda (Tapeworms).—The tapeworms are ribbon-like animals made up of segments and varying from a few millimeters to several meters in length. They are exclusively parasitic, and as a result have become greatly modified in structure; there is no trace of mouth or any other part of the alimentary canal, and they are nourished by the partly digested food of their host, which they absorb through the skin. Firm adhesion to the host's intestine is necessary in order to avoid the loosening action of peristalsis as the food passes along, which is provided for in various ways.

The question as to whether a tapeworm is a single animal or a colony of animals is still in dispute. According to the older view, a tapeworm is a colony of two generations—the head and neck produced by the larva, and the joints or *proglottides* produced by segmentation from the head. More recently the view that there is but a single animal has been advanced. The “ripe” proglottides are expelled with the feces or they escape spontaneously (Fig. 111). They are literally stuffed with eggs, which are liberated either by decomposition of the proglottides or by some animal swallowing the latter. The embryo has three pairs of hooks (hexacanth), and by means of these it bores through the alimentary canal of its host, having previously lost its covering, which was dissolved by the gastric juice. Once through the intestine, it makes its way to the tissue in which it is apt to become encysted—in the muscles, connective tissue, liver, or other viscus—and awaits here a transfer to the final host. Man harbors most tapeworms, both in the adult and larval stages; the *Tania echinococcus* is found only in the larval form in human subjects.

Tania saginata (*T. mediocanellata*), the *unarmed* or *beef tapeworm*, has an average length of 8 to 10 meters. The head is 1.5 by 2 mm., large enough to be seen by the naked eye and frequently colored dark gray or black. The top is plane or even slightly concave, and has four powerful sucking disks, but no hooks. A rather long neck succeeds the head, and then comes the body proper, consisting of 1200 or more segments (Fig. 111). The first segments have no traces of sexual organs; the testes are the first to appear, farther along are the female organs, and finally the ova in the segments farthest from the head. The six-hundredth segment would be about the first to show any sign of sexual organs, the ova appearing about the one-thousandth segment, and the last 100 or 200 are ripe segments.

The sexually mature segments are greater in length than in breadth; the largest segments are not at the extreme end of the chain, for these have been partly emptied of eggs.

The head is fixed to the mucous membrane of the intestine close to the pylorus, and, while not armed, is harder to expel than the armed species.

Usually only a single worm is present, although as many as twenty-five have been found. (Of 2686 patients in the French naval hospitals, 2341 or 89 per cent. had only one tapeworm—Berenger-Feraud.) They are seen in patients of all ages, from nurslings to persons of over eighty years, most of the patients being between twenty and fifty years of age.

The larval form is the *Cysticercus bovis*, which is found in the connective tissue of the striped muscles and occasionally in the viscera of cattle; hence man is infested by eating raw or partly cooked beef (Fig. 110). The duration of life of the cysticerci is not accurately known, but they probably live for several months or even years.

FIG. 110.—Life cycle of *Tænia saginata* (after Bollinger).

In the ox the cysts are round, small, less than 1 cm. in length, and few in number. They are not found in man, although two or three doubtful cases are reported. After the cyst is swallowed, two or three months elapse before the segments appear. From Perroncito's experiments, it is probable that the worm grows to about 72 mm. and produces 13 to 14 segments daily.

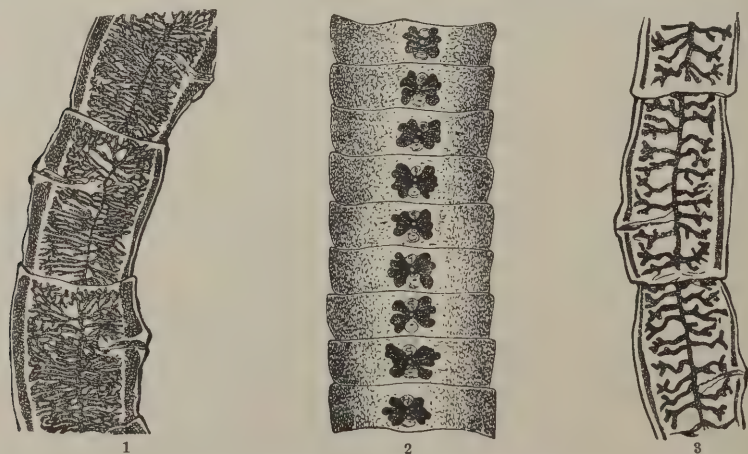


FIG. 111.—Segments of (1) *Tænia saginata*, (2) *Bothriocephalus latus*, and (3) *Tænia solium*, showing the arrangement of the uterus.

The beef tapeworm is cosmopolitan and is found wherever beef is eaten, though the percentage of affected individuals varies greatly. Thus it is very common in Eastern Europe, India, and Abyssinia, so much so in the latter country that each adult native is supposed to harbor one or more individuals; in Western Europe and the United States it is less common.

The life of the worm may continue for many years with daily formation of segments. The latter escape singly, and, owing to their well-developed musculature, are able to crawl about the patient's bed, his clothes, or even the walls of the room.

Tenia solium, the armed or pork tapeworm, is a comparatively short worm of 2 or 3.5 meters, rarely 7 or 8 meters, in length. The head is rounded, much smaller than in the preceding, 0.5 to 0.7 mm. in diameter, and provided with a retractile proboscis or rostellum, occasionally colored gray or black. About the circumference of this rostellum are two circles of small hooks, the total number varying from 26 to 32; below the circle of hooks are four sucking disks. The neck is filiform; the body is composed of 850 to 900 segments, which when mature measure from 9 to 10 by from 4 to 6 mm. The sexual organs begin to appear about the three-hundredth segment, and, while the last 80 or 100 segments only are ripe, they make up one-third of the total length. Several segments are voided together instead of singly as in *T. saginata*; they are also not so mobile as those of the latter. The worm is found in the small intestine, adhering to the duodenum or jejunum and extending down toward the ileocecal valve.

The pork tapeworm is also cosmopolitan, though it is becoming less frequent since the discovery of the *Trichina spiralis* and the greater care taken in cooking pork. It is especially rare in the United States. According to Blanchard, for every 1000 specimens of *Tænia saginata* met with in Paris, only 21 specimens of *Tænia solium* occur. The larval form (*Cysticercus cellulosæ*) is found in the pig and various other animals, and, contrary to the usual rule, both larva and adult may develop in man (Fig. 112). Nearly three dozen cases are known of patients harboring *Tænia solium* and *Cysticercus cellulosæ* at the same time.

Cysticercus cellulosæ, the larval form of the armed tapeworm, is the "measles" of pork. It is an oval, translucent vesicle, 8 to 12 mm. in length, found in the connective tissue, especially of the muscles of the tongue, neck, and shoulder, though it may invade nearly every organ. When insufficiently cured or cooked pork is eaten, the larva is set free after solution of the capsule in the gastric juice, the head attaches itself to the mucous membrane, and the adult stage begins. About three months elapse before this is complete.

In man, cysticerci are found in various parts of the body; they are more common in the upper half, and appear to be symmetrically distributed. Large numbers are sometimes found; thus Lancereaux reports a case where over 1000 could be detected subcutaneously. The apparent predilection of

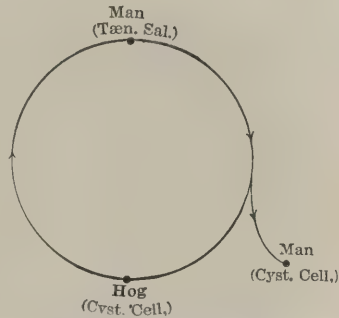


FIG. 112.—Life cycle and intermediate hosts of *Tænia solium* (after Bollinger).

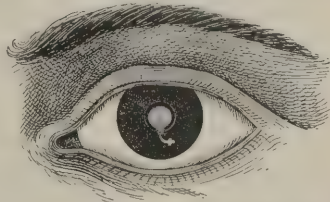


FIG. 113.—*Cysticercus* of the anterior chamber of the eye (Blanchard).

the cysticerci for the brain and the eye is probably explained by the fact that they soon excite symptoms in these locations, while elsewhere they may give rise to none (Figs. 113, 114). In the subcutaneous tissues they form small painless swellings, from the size of a bean to that of a walnut. In the brain they develop into irregular branching forms sometimes called *Cysticercus racemosus*. Cysticerci of the bones and lymph-glands are exceedingly rare, only 2 cases of each being on record. Of 43 cases of cyst of the

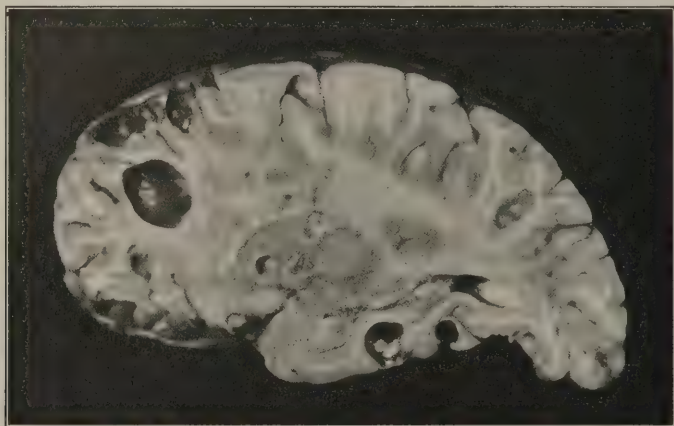


FIG. 114.—*Cysticercus cellulose* in the human brain.

cerebral ventricles, 61 per cent. were in the fourth ventricle (Verdun and Iversen¹). In connection with a case of cysticercus of the brain, Diamond² was able to collect only 8 cases of cysticercus in any part of the body reported from America, and none of them probably originated in this country.

Individual segments of *Tænia solium* may be distinguished from those of *Tænia saginata* by the uterus having in the former from 6 to 13 ramifications instead of from 20 to 30 in the latter. If the ramifications are not easily discerned, the segment can be placed in a weak potash solution (1 per cent.) or 20 per cent. acetic acid to clear it up, and then pressed between two microscopic slides and held to the light.

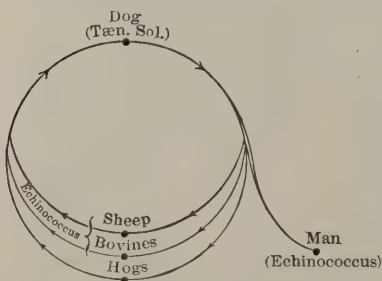


FIG. 115.—Life cycle and intermediate hosts of *Tænia echinococcus* (after Bollinger).

Tænia echinococcus is a small worm, 2.5 or 3.5 mm. in length. The head has a long, prominent rostellum with a double circle of hooks, from 30 to 40 in number; below the hooks are four suckers. The body

is composed of only three or four segments, the last being equal in length to the others combined.

¹ *Arch. de Parasitologie*, i., 344, 1898.

² *Jour. Amer. Med. Association*, p. 1365, June 17, 1899.

While this species has been found in the wolf and jackal, its usual host is the dog, in which it may be found sometimes by thousands in the upper part of the small intestine (Fig. 115). In Iceland, Krabbe found it in 28 per cent. of the dogs; it is also extremely frequent in Australia; elsewhere it appears to be scarce. In man, only the cystic form is found.

The bladder-worms of the two preceding varieties each produce but one head, while those of the present species may produce many. Three varieties of cyst-formation are known:

Echinococcus scolicipariens (*E. veterinorum*, *E. granulatus*).—The embryo, being set free in the stomach, penetrates the mucous membrane and is carried to various organs by the lymph or blood current. When finally lodged, a cyst develops about it—the *hydatid* or *echinococcus* cyst. This is small at first, and the wall is composed of two layers—an outer or cuticular layer which is laminated, and an inner or parenchymatous layer which is granular and contains muscular fibers. Small buds—"brood capsules"—appear in a few weeks, projecting from the inner layer; these become hollow in the center, and from these brood capsules the tapeworm-heads (scolices) grow, some 15 or 20 in number in each capsule (Fig. 116). The scolices project at first, later they are invaginated into the capsule. Sometimes they become

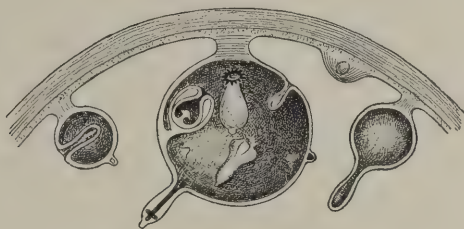


FIG. 116.—Section of *Echinococcus scolicipariens* (Braun).

loose and float about in the interior. The original cyst increases in size by the growth of the capsules, and the cyst-cavity is filled with hydatid fluid. Occasionally the original cyst produces no buds, and it is then known as an "acephalocyst." The *scolicipariens* variety is found chiefly in animals, but also occurs in man.

Echinococcus altricariens (*E. hominis*, *E. hydatidosus*).—In this variety the cyst is much larger, separate "daughter"-cysts are enclosed in the original cyst and are sometimes very numerous, several hundred or a thousand or more. "Granddaughter"-cysts frequently develop in the daughter-cysts, and even a fourth generation may be produced. This variety is found principally in man.

Echinococcus multilocularis is rare, less than 100 cases being known. At first it was thought to be a colloid carcinoma, until its true nature was recognized by Virchow. It consists of a large tumor-like mass, which on section shows numerous small round cavities filled with gelatinous fluid; the center is often broken down into a large cavity, and scolices are rarely found (Fig. 117). The geographical distribution is very peculiar, and only 1 case is known in America. Of 80 cases, 29 occurred in Bavaria, 21 in Switzerland, and 18 in Würtemberg. Most of the cases occur in women, and in the right lobe of the liver.

Echinococcus cysts are found in tissues having a good blood-supply, and rarely in unstriped muscle. They are especially frequent in the liver (57 per cent. of all recorded cases); the lung comes next in frequency, then the kidney, spleen, etc. Several organs may be invaded simultaneously. The female sex is more often affected (58 per cent., Neisser). They are found between the ages of ten and fifty.

The pathologic effects of the cyst are due to direct pressure; as it grows, a connective-tissue capsule develops about it, although in cysts growing into

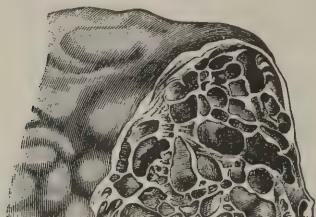


FIG. 117.—*Echinococcus multilocularis* (Luschka).

the body-cavities this may be wanting. They may open on the surface of the body, into various cavities, or into the hollow viscera. Suppuration may occur in the contents, or the parasite may die; the contents of the cyst become caseous and finally calcareous.

Hydatid fluid is colorless, odorless, neutral in reaction, with a specific gravity of from 1006 to 1015.

The solids vary from 1.2 to 1.4 per cent., and consist of sugar and inosit; traces of urea and creatin, sodium chlorid (0.61), and other salts. The pure fluid contains no albumin. It has been known for some time that exploratory or other puncture of a hydatid cyst gives rise to toxic phenomena. Boinet and Chazoulière¹ have found this to be due to a ptomain isolated and studied by them.

If the hydatid tumor be grasped by one hand and percussed with the other, a peculiar vibration will be transmitted, which was supposed by its discoverer, Briançon, to be due to the daughter-cysts striking each other while floating. This is the "hydatid thrill" or fremitus, and it is of much less value in diagnosis than was formerly supposed. It is absent in about half the cases, especially when the cyst is solid or deep-seated, and is found also in ascites



FIG. 118.—*Dipylidium caninum* (Mosler and Peiper).

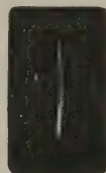


FIG. 119.—*Hymenolepis murina*, about natural size (Mosler and Peiper).

and ovarian tumors. Bamberger claims it is even more frequent in the latter conditions.

The distribution of hydatid cysts agrees with that of the echinococcus tapeworm. They are very frequent in Iceland and other parts of Europe.

¹ *Rev. de Med.*, p. 845, 1898.

In this country only about 100 cases are on record (Sommer)¹; of these, 33 occurred in New York:

Dipylidium caninum (*Tænia cucumerina*, *T. elliptica*) is a tapeworm from 15 to 35 cm. in length. The head has three or four circles of hooks, from 40 to 60 in number, with four suckers. The neck is filiform; the mature segments, of which there are about 25, are much longer than they are wide (6 to 7 by 2 to 3 mm.), and are of a reddish color from the contained eggs; the genital pore is bilateral (Fig. 118). This species is very common in the dog, and is found in about half the individuals examined. The dog-louse, and occasionally the dog-flea, is the intermediate host. Some two dozen cases have occurred in man, the majority in children.

Hymenolepis murina (*Tænia nana*), the smallest tapeworm infesting man, is from 8 to 15 or 20 mm. in length and from 0.5 to 0.7 mm. in width. The head is from 0.26 to 0.29 mm. in diameter, somewhat

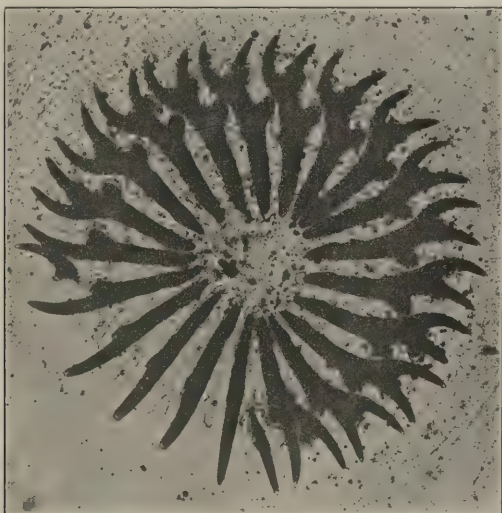


FIG. 120.—*Hymenolepis murina*, showing circle of hooks.

spheric, with a rostellum, a single circle of 24 to 28 hooks, and four powerful sucking disks; the neck is filiform (Fig. 119). The segments are 190 or 200 in number, the last 40 or 50 being mature. The ripe segments are yellowish brown from the contained eggs; the genital pore is on the same side of all the segments. This is a common species in rats and mice, and the former are probably the source of infection. Grassi has shown that in the rat the embryos become encysted in the mucous membrane of the intestine, the cyst ruptures and the animal falls into the intestine, completing its development there. In man it is seen chiefly in children and youths, attaching itself deeply; from 40 to 5000 individuals are found. As rats and mice are met with throughout the world, this species is probably also cosmopolitan. It was discovered in Egypt and is frequent in warm countries, in Siam, Brazil, Buenos Ayres, and in Germany and Italy.

¹ *N. Y. Med. Jour.*, p. 656, Nov. 23, 1895; also, p. 263, Aug. 22, 1896.

Hymenolepis diminuta (*Tenia flavopunctata*).—This is a small tapeworm, 20 to 40 cm. long; its head is very small, cuboidal, with a rostellum and four small suckers, but no hooklets; the neck is filiform. The segments number 1000 or more. The old name was derived from the distended receptaculum seminis, which shines through the anterior segments as a yellow spot; further back the segments become brown from the contained eggs. Nearly every other segment is sterile; the genital pore opens on the same side in all segments. It is a parasite of rodents, especially the house-rat, while the larva is found in insects. It has been seen six times in human beings, always in young children, and the number present was from one to six worms.

Davainea madagascariensis (*Tenia madagascariensis*).—This tapeworm is from 25 to 30 cm. long, the head being round, with a rather large rostellum, and four suckers arranged in two pairs joined to each other; there are no hooklets. The body contains from 500 to 600 segments; the genital pores are on one side, and the eggs are in round masses arranged in transverse rows. Nine cases are on record, all but one in children from Comoro, Mauritius, British Guiana, and Siam.

Bothriocephalus latus, the broad tapeworm, is the longest species infesting man, and measures from 6 to 10 meters or more in length. The head is club-shaped, 2 to 2.5 mm. long by 1 mm. wide; there is no rostellum or hooks, and the sucking disks of the preceding species are replaced by two long and deep grooves, one on each lateral border (Fig. 122). The neck is

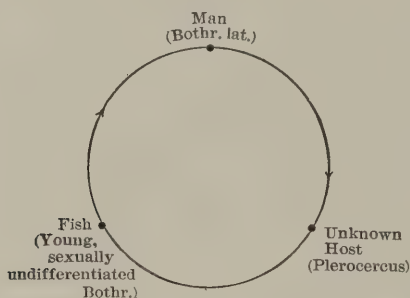


FIG. 121.—Life cycle and intermediate hosts of *Bothriocephalus latus* (after Bollinger).

narrow; the segments, 3000 to 4000 in number, are short and very broad, 10 to 15 by 3 to 4 mm. The genital pores are not on the edge, but on the flat surface in the center of the segment, and are always on the same



FIG. 122.—Head of *Bothriocephalus latus*: a, bothridies; b, neck (Blanchard).

side. The eggs are 0.68 to 0.70 by 0.044 to 0.045 mm., elliptical, brownish, with a lid at one end which becomes more prominent as development advances. They develop in water, slowly; the embryo is ciliated and swims about until it finds a host (Fig. 121).

The broad tapeworm is difficult to expel, and has been known to live in the body for fifteen or more years. But one individual is present, as a rule, though as many as 90 have been voided. About six weeks are required for complete development after the embryo is swallowed. Man may be infested at all ages, and the worm may be found in company with other species of tapeworm. The intermediate host is furnished by various species of fish, especially the pike and burbot (79 of 80 fish examined at Dorpat were found to be infested), and in Japan a salmon (Fig. 123). There are two main centers of infection: (1) The region about the Swiss lakes, including Bavaria and North Italy. (2) The shores of the Baltic—Pomerania, Sweden, Finland, Russia (15 per cent. of inhabitants of St. Petersburg are said to be affected). It occurs sporadically in Belgium, Holland, Japan, and elsewhere.

Bothriocephalus cordatus is a comparatively short tapeworm about 1 meter long, with a heart-shaped head. It is a frequent parasite of the seal, walrus, and dog, in Greenland, and was found there once in a woman.

Bothriocephalus Mansonii (*Ligula Mansonii*) has been found only in man, and in the larval state. The larva is 30 to 35 cm. in length, with transverse striations. It is found in the subperitoneal tissue, in the subcutaneous tissue, under the conjunctiva, and was once expelled through the urethra. It is met with in Japan, China, Australia, and British Guiana.

Krabbea grandis is a long worm, the total length being probably 10 meters or more; the segments are extremely short (0.45 mm.); the head has not yet been found. The sexual organs open into two long grooves on the ventral surface. Discovered by Ijima in a Japanese man, aged 28, who had suffered for years from colic, vertigo, and a progressive anemia which disappeared with the evacuation of the worm. This species may prove to be a parasite of the seal, as the discoverer states that it resembles species of *Bothriocephalus* found in that animal. This view is rendered probable by the known occurrence of *B. cordatus* and *A. maritima* both in man and in the seal.

Anomalies.—*Tænia saginata* and *Bothriocephalus latus* are most frequently malformed. The segments are principally affected; sometimes many are coalesced into one (*Tænia fusa*). Supernumerary segments may be met with, also various anomalies in the number of the genital pores, or even inversion; e. g., in *Bothriocephalus latus* the male organs may be on the edge instead of on the side. Ripe segments are sometimes so full of eggs that they burst, and a ring of tissue is all that is left of the segment (*Tænia fenestrata*) (Fig. 124). The whole worm may be colored dark gray or black by the bile, blood, or medicinal agents (*Tænia nigra*). *Bothriocephalus latus* with a malformed head was described as *B. cristatus*. A prismatic form has been known for over a century. Cattaert¹ proves that it is due to the fusion of two individuals. If the fusion is by edges, a V-shaped form results; if the fusion is more complete, a Y is produced. The head is invariably furnished with six suckers, and the embryos also are malformed.

Symptoms of Tapeworm.—In many cases none are appreciable, in other instances various nervous and digestive disturbances result. Probably the



FIG. 123.—Plerocircoid of *Bothriocephalus latus*: a, with head projected; b, with head retracted (Braun).

¹ *Arch. de Par.*, ii., p. 153, 1899.

psychic effect has some influence, for many patients suddenly become affected after discovering the passage of the segments. Berenger-Feraud gives a long list of ailments supposed to result from the presence of tapeworms. Among the nervous manifestations may be mentioned: epilepsy, chorea, giddiness, amaurosis, and hallucinations. On the part of the digestive tract: nausea, colic, constipation alternating with diarrhea. Boulimia, in the popular mind, is one of the chief symptoms; but professional experience shows this to be unfounded. The species found principally in young children cause more marked symptoms—convulsions, etc.—on account of the more susceptible age. *Bothriocephalus latus* gives rise, in addition, to a severe form of pernicious anemia—"Bothriocephalus anemia," which arises from intoxication by some poison given off by the worm. Such an anemia is sometimes found when *Tænia saginata* is present, but not with *Tænia solium*. Tapeworms occasionally escape through the bowel and are found in the peritoneal cavity; this occurs *always* through a pre-existing perforation.

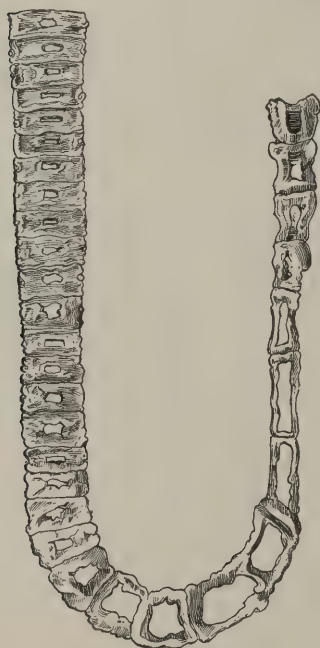


FIG. 124.—*Tænia fenestrata* (after Léon Colin).

a rule, is smaller. The embryos in most cases are lodged in an intermediate host; in some the definitive host is directly attacked by them.

Ascaris lumbricoides, the common round worm, is a parasite of the small intestine. The male is from 15 to 25 cm. in length, the female from 20 to 40 cm.; the latter is also thicker and three or four times as abundant. The body is yellowish gray or reddish in color, with fine transverse striations; the anterior end is furnished with three papillæ. The posterior extremity of the male is recurved and provided with two spicules; that of the female is plane and without spicules. The eggs are easily recognized (Fig. 125) and very numerous in the feces; they measure from 0.05 to 0.06 mm. in length and have a thick shell enclosed in a brown albuminous capsule. The eggs develop very slowly and may live for five years in a suitable environment.

This species is rarely found single, two to six individuals being usually met with, and from this up to from 300 to 500. It is very often seen with other parasites, especially the other round worms. From 1 to 5 years of

The **Nemathelminthes** or round worms have a cylindric body, with the organs contained in a body-cavity. Of the three branches composing them, one is known to be parasitic in man; the other two are uncertain.

Nematoda (*Round Worms*).—The nematodes or round worms proper have long bodies which are not segmented, though sometimes there are external striations. They usually taper off at each end and are provided with a mouth and digestive tract ending in an anus.

The sexes are separate; and the male, as

age, the percentage of individuals affected is 10.09 ; from 15 to 20, 27.58 ; and from 45 to 50, 15.12. The round worm is greatly given to wandering and may get into the stomach, nares, glottis, Eustachian tube, pancreatic and biliary ducts. It may perforate the alimentary canal and escape into the urinary organs or through the walls of the body after an abscess has been formed—about the umbilicus in children, the groin in adults. No intermediate host is necessary ; infection occurs through swallowing the eggs in water or food, or through geophagous habits in young children when creeping about. In many cases no symptoms are produced, especially if but few individuals of the worm are present. In young children and nervous individuals it causes considerable disturbance, both reflex and direct—convulsions, vertigo, impaired sight and hearing, colic, vomiting, itching of the nose, etc. In the biliary passages it produces obstruction, then dilatation, with structural changes and jaundice. Sometimes large masses of worms accumulate, giving rise to intestinal obstruction and requiring laparotomy, as in a recent case of Wyeth's (New York). The round worm is cosmopolitan, extremely frequent in some countries (90 per cent. of the Japanese are

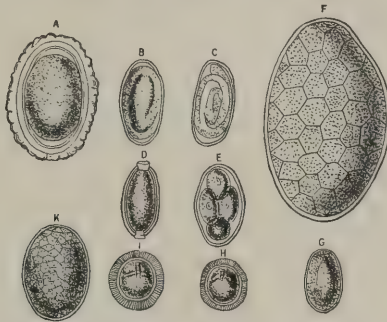


FIG. 125.—Eggs of various worms found in the alimentary canal of man: A, *Ascaris lumbricoides*; B, C, *Oxyurus vermicularis*; D, *Trichocephalus dispar*; E, *Ankylostoma duodenale*; F, *Fasciola hepatica*; G, *Dicrocoelium lanceolatum*; H, *Tænia solium*; I, *Tænia saginata*; K, *Bothriocephalus latus*. $\times 400$.

affected, Bälz), especially in the tropics ; its frequency diminishes as we leave the equator. It is more common in country districts, owing to the use of unfiltered water ; and Blanchard states that in the early part of the century one-half the inhabitants of Paris were infested with the worm from this cause.

Ascaris canis (*Ascaris mystax*) is a common parasite of the small intestine of the cat, dog, and other carnivora. This species is smaller than the preceding, the male being from 40 to 60 mm. in length and the female from 60 to 100 mm. It is easily distinguished by two wing-like folds from 2 to 4 mm. in length, one on each side of the anterior extremity. Eight cases of its occurrence in man are known, but no serious symptoms appear to be produced.

Ascaris maritima has been found as an immature form in a child in Greenland.

Oxyurus vermicularis, the *seat- or pin-worm*, is a small species, the male being about 4 mm. in length and the female about 10 mm. The posterior end of the male is blunt and curved, that of the female is sharp (Fig. 126). The egg is 0.050 by 0.024 mm., oval and flattened on one side. No intermediate host is necessary ; hence, like *Ascaris lumbricoides*, it is sometimes

endemic in barracks, prisons, and similar communities. The seat-worm is more common in children and in females, and with other parasites is found frequently in immense numbers in the small intestine and occasionally in the appendix. After the females have become impregnated, they descend to the large intestine. Individuals often escape from the anus and penetrate to the prepuce and urethra, and to the vulva, vagina, and even into the uterus. This species gives rise to bloody diarrhea and to various nervous symptoms already alluded to in considering other worms. The principal manifestation is an intolerable pruritus coming on after the patient is warm in bed, which is due to the irritation kept up by the sharp tail of the female. This leads to eczema and masturbation in some cases. As reinfection easily



FIG. 126.—*Oxyurus vermicularis*: a, female; b, male (natural size) (Mosler and Peiper).

occurs through the fingers, the parasite may persist for many years or for life. The worm is found throughout the world.

Eustrongylus visceralis (*E. gigas*), the giant strongyle, is a very long worm inhabiting the urinary organs of various mammals, especially the dog. The body is reddish, cylindric nearly throughout, the male being from 15 to 35 cm. in length, the female from 25 cm. to 1 meter. The male has a single spicule at the end of a copulatory pouch which is easily recognizable. The kidney is sometimes entirely destroyed by the parasite. Blood-clots passed by the urethra are frequently mistaken for it. It is found in many parts of Europe, North and South America, but is nowhere common. Nine or ten cases of its presence in man are on record.

Strongylus apri (*S. paradoxus*, *S. longæ-vaginat*), a small white worm found in the lungs of the hog; the male is 15 to 17 mm. in length, with two spicules at the posterior end, the female 26 mm. It was found once in the lungs of a child, and once in the alvine discharges of an adult.

Strongylus subtilis is a very slender worm recently discovered by Loos in Egyptian natives. The male is about 4 mm. long, the female 7 mm. Its habitat is the upper part of the small intestine, where the females are much more abundant; the mouth is unarmed. No pathologic effects are attributed to it.

Ankylostoma duodenale (*Uncinaria duodenalis*, *Dochmius duodenalis*), the cause of ankylostomiasis, "miners' anemia," "tunnel disease," or Egyptian chlorosis, is a very small round worm, the male from 6 to 11 mm. in length, the female from 15 to 18 mm. (Fig. 127). The color varies from white to red, according to the amount of blood in the body. The head is provided with six teeth and a sucking apparatus. This species inhabits the small intestine and is usually found within two meters of the pylorus, occasionally two or three meters lower down, seldom in the stomach. The head and often part of the body are firmly buried in the mucous membrane, and



FIG. 127.—*Ankylostoma duodenale* (natural size) (after Schultheiss): a, b, c, females; d, e, f, males.

sometimes cannot be dislodged even at a necropsy. Sandwith, of Cairo, who has had unusual opportunities for observing ankylostoma, found 863 individuals to be the maximum in 400 cases.¹ They are, however, often

¹ *London Lancet*, p. 1862, June 2, 1894.

found in much larger numbers—into the thousands. Grassi calculates that for every 150 or 180 eggs in a cubic centigram of feces, 1000 worms are present. The proportion of males to females is about 1 to 3. The worm is supposed to live several years. Infection occurs from earth containing the embryos being carried to the mouth, either on the hands or with the food. Drinking-water seems to be a less important source of danger.

This species, though small, is one of the most formidable parasites infesting man. It is widely distributed in Italy (in 20 per cent. of the necropsies in Milan), Switzerland, Germany, Austro-Hungary, Egypt, Abyssinia, India (75.5 per cent. of 1249 natives, Dobson), Japan, Borneo (100 per cent.), Java; also in Brazil, Guiana, the Southern United States, and Porto Rico. If few worms are present, the pathologic effects are not marked; if many hundreds are present, a grave anemia with the characteristic signs appears.

In discussing this anemia, Rogers¹ shows that it is characterized by: 1. A much greater reduction of hemoglobin than of the number of red corpuscles, and consequently a very low hemoglobin value. 2. The white cells also are reduced in number, but relatively to the red cells they are increased. 3. The specific gravity is greatly reduced after allowing for the amount of reduction of the hemoglobin. In 12 cases the per cent. of hemoglobin averaged 15.16. The red cells were 2,145,000 per cubic mm., the hemoglobin value of each red corpuscle being only 0.31 as against 0.65 for healthy natives or even those suffering from malarial anemia; so these two anemias can be differentiated. The ratio of white cells to red cells was as 1 to 524, and the specific gravity was 1034.

The local changes are thickening of the mucous membrane, with mal-assimilation and chronic starvation. Pure blood is not seen in the stools, and bloody mucus only occasionally, the blood being so mixed with the bowel contents that it is seldom distinguishable.

Trichocephalus dispar (*T. trichiurus*, *T. hominis*), the whip-worm, has a body composed of two unequal parts; the anterior three-fifths is no thicker than a thread and contains only the esophagus; the posterior two-fifths is

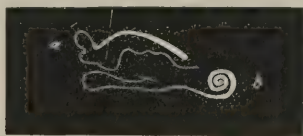


FIG. 128.—*Trichocephalus dispar*: a, female; b, male (natural size) (Heller).

much thicker. In the male it is wound up into a spiral, in the female it is slightly curved; the total length of the former is from 35 to 45 mm., of the latter from 35 to 50 (Fig. 128). The usual habitat is the cecum, also the appendix and the first part of the colon. While generally free in the bowel, the anterior end often transfixes the mucous membrane like a pin. From 6 to 20 individuals is the rule, sometimes 150; rarely more are found. Both sexes are affected, and all ages except very young children. No intermediate host is required, and Grassi infested himself by swallowing the eggs; after a month's time he discovered eggs in his stools. The whip-worm is

¹ *Jour. of Pathol. and Bacteriol.*, v., p. 399, 1898.

cosmopolitan in distribution and extraordinarily frequent in hot climates (90 per cent. of the inhabitants of Cachar, India, are affected—Powell). As a rule, no pathologic effects seem to be caused by this species, although occasionally it excites the usual reflex nervous symptoms. Rokitsansky believed it to be the cause of enteric fever.

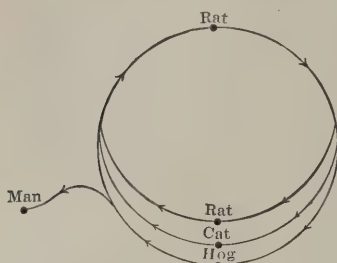


FIG. 129.—Life cycle and intermediate hosts of *Trichina spiralis* (after Bollinger).

Immediately after infection, the males are less numerous and soon die, leaving females alone present. In three or four hours after eating raw or insufficiently cooked pork, the young worms are found in the stomach; they pass hence to the small intestine, arriving at sexual maturity in three or four days (Fig. 129). Many of the embryos escape with the feces; the others ultimately rest either in a muscle-fiber or between the fibers.

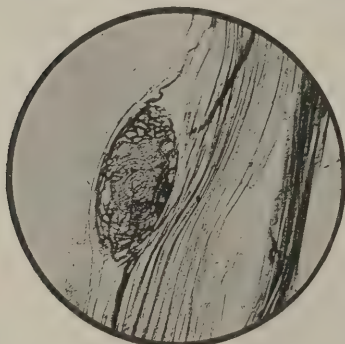


FIG. 130.—*Trichina spiralis* encysted in muscle. Teased fresh specimen.

The capsule containing the muscle-trichina is about 0.40 mm. in length, usually oval, sometimes round, parallel with the long axis of the fibers (Fig. 130), and at first clear, but eventually calcified. Only one worm is found in a capsule, as a rule, though as many as seven have been met with; one gram of muscle has been estimated to contain from 12,000 to 15,000 embryos. The cysts may live for many years without becoming calcified—in man 12 years, in the pig 11, 20, and 24 years; they survive exposure to extreme heat and cold ($+80^{\circ}$ and -25° C.).

Two views are held as to the origin of the cyst: one that it is formed by the

sarcolemma, the other that its presence causes proliferation of the connective tissue. The old view that the embryos bore their way through the intestinal wall has been disproved by Askanazy and Cerfontaine, who found that the female itself penetrates the wall and the embryos are born directly into the lymph-current.

When the embryos are first freed they give rise within a day to intense gastro-intestinal irritation with vomiting and diarrhea, the attack bearing some resemblance to enteric fever. On their migration they cause myositis with severe muscular pains and high fever. At first there is edema of the face, especially of the eyelids; later on of the trunk and limbs, not involving the genital organs. The attack is at its height in two to four weeks after infection, and either death or subsidence occurs. The muscles of the upper

half of the body are more frequently the location of the cysts—the diaphragm (especially its pillars), the intercostal and lumbar muscles, the tongue and eye; the heart seems to escape. In the muscles they are found mostly at the tendinous ends, and are less numerous in the limbs as the periphery is approached. Besides muscles, lymph-glands are also involved. As the hosts of the trichina—the rat and hog—have a world-wide distribution, it also has a wide range, but great local differences exist. Thus it is not frequent in England, France, or Italy. It is common in Holland, in Germany (of 4,421,208 hogs examined in Prussia in 1885, 2387 had trichiniasis), and in the United States (estimated at 2 to 3 per cent. of hogs). The German custom of preparing dishes from partly cooked pork has been responsible for many so-called “epidemics.” Two of the most destructive occurred in Saxony. In 1865, in the village of Hedersleben, with a population of 2000, 337 persons were attacked, with 101 deaths. In 1884, in the villages about Emersleben, with a population of 1600, the flesh from one hog gave rise to 256 known cases, with 52 deaths.

An important diagnostic point in trichiniasis is the discovery by Brown¹ of a marked increase of eosinophilic cells in the blood, which can be made use of at once. Osler shows that sporadic cases are much commoner than hitherto supposed, and that the eosinophilia is an important point in diagnosing obscure cases.

Filaria medinensis (*Dracunculus medinensis*), the guinea-worm, the cause of dracontiasis, has been known since the days of Moses, for it is evidently the “fiery serpents” mentioned in the Bible. The male has only lately been discovered and is much smaller than the female, which is from 60 or 80 cm. to 1 meter in length. The body of the latter is yellowish white in color, very extensile, and consists mostly of the uterus, which is closely packed with small embryonic worms. The connective tissue in any part of the body is the habitat of this species, and while as many as thirty have been seen in the body at one time, a single worm is the rule. In 98 or 99 per cent. of the cases the worm appears in the lower limbs. (In a patient with seven worms, three were in left leg, two in left foot, one in right leg, and one in right forearm. In another with thirteen, four were in left foot, two in right foot, two in left leg, one in right leg, one in right thigh, and three in right forearm—Lorimer.) It may appear anywhere—orbit, mouth, ears, eyelids, etc., but these locations are very rare. The female, when mature, wanders through the tissues until the skin is reached; a small vesicle forms over the head, which ruptures in a few days, revealing the worm at the bottom. The embryos are discharged through this for a week or two, by which time the uterus is empty and the parent quits the host or can be extracted. Clumsy attempts at extraction—rolling up the worm on a stick, etc.—frequently pull it in two, with disastrous results; for the embryos, escaping into the tissues, cause abscess-formation, sloughing, and the limb very often requires amputation. Fedtschenko has proved that the embryo penetrates the familiar fresh-water crustacean Cyclops and becomes metamorphosed in a month. Hence drinking-water is probably the means of infection. In man the worm requires a year or eighteen months to attain maturity. The guinea-worm is widely distributed in the tropical regions of Asia and Africa, also in Brazil.

Filaria Sanguinis Hominis.—Under this name, Lewis, of Calcutta, in 1872 described a parasite of human blood which was first noticed in 1863

¹ *Jour. Exper. Med.*, iii., p. 315, 1898.

by Demarquay. We owe to Manson's researches the discovery that there are five or six different species included under this designation. Some of these are found in the blood at night, others in the day, and still others all the time. The periodicity in the nocturnal forms is constant; it continues night after night with unfailling regularity for years. Its object, according to Manson, is to adapt the habits of the parasite to those of its intermediate host, the mosquito. The same observer discovered that the embryos which leave the cutaneous circulation in the day are found partly in the larger arteries, but the vast majority in the pulmonary blood-vessels.

Filaria Sanguinis Hominis Nocturna.—The embryo is about 0.3 mm. in length, transparent, with a pointed tail, and enveloped in a sheath which is longer than the animal and projects beyond it at one or both ends (Fig. 132). This species is found in both tropical and temperate climates, in the latter in new arrivals from warm countries. It is especially frequent in some districts—Bahia (10 per cent. of population), Cochín-India (30 per cent.), Samoa and Fiji (50 per cent.—Thorpe). In the United States it is found in Virginia, South Carolina, and Alabama. The filariæ appear in the cutaneous circulation about five or six o'clock in the evening, and increase up to midnight; after that they gradually decrease until by eight or nine o'clock in the morning they have nearly all disappeared, to come forth in the evening again. If the sleeping and waking hours be reversed, the filarial periodicity is also reversed. As many as 300 parasites have been found in a single drop of blood; they are also found in the urine and tears.



FIG. 131.—*Filaria sanguinis hominis*, adult female (natural size) (after Cobbold).

The female mosquito acts as the intermediate host. The parasites in the cutaneous circulation are sucked up and enter the body of the mosquito, where they are metamorphosed. In about a week's time they escape into the water, on the death of the mosquito after laying its eggs. Gaining access to the human stomach in the drinking-water, they bore through the tissues and become sexually mature in the lymph-vessels, whence the embryos are carried into the blood through the thoracic duct.

Filaria Bancrofti is the parent form of *F. nocturna*, and inhabits the lymph-vessels. The male is transparent and about 70 mm. in length; the female is brownish, very thin, and measures 90 mm. (Fig. 131). Embryo filariæ (*F. nocturna*), so far as known, cause no pathologic effects, but *F. Bancrofti* produces marked changes by blocking the lymphatics. If the occlusion is only partial, a lymph-varix is the result, evidenced by lymph-serotum, varicose lymphatic glands, chyluria, chylous ascites, or chylous accumulation in the tunica vaginalis. When the obstruction is complete, the lymph-trunks may burst with ensuing lymphorrhagia, or the lymph accumulates in the tissues, which are first edematous, then firmer, and elephantiasis Arabum develops.¹

Filaria sanguinis hominis diurna is a worm known only in the embryonic state, in which it is very similar to *F. nocturna*, and is found in negroes on the west coast of Africa. Unlike the latter, it is only present in the blood in daytime, commencing to appear at eight or nine o'clock in

¹ For illustrative case, see Report of Two Cases of Filariasis, by Lothrop and Pratt, *Am. Jour. Med. Sc.*, cxx., p. 525, 1900.

the morning, increasing until noon, and disappearing about eight or nine o'clock in the evening. It is said *Filaria loa* is the parent form of this variety. The intermediate host must evidently be some diurnal species, but the exact one is unknown as yet.

Filaria loa is about 25 mm. in length in the male, and 30 to 40 mm. in the female. It occurs in the subcutaneous connective tissue and is often found about the bridge of the nose, also under the conjunctiva. It is a native of the west coast of Africa, occurring over the same area as its supposed embryo, *Filaria diurna*. It has been noticed in persons absent from that country for over ten years. When located in the eye, it causes great pain.

Filaria sanguinis hominis perstans is much smaller than the other filariæ, both in length and thickness. It is about 0.25 mm. in length, has no sheath, but is provided with a retractile proboscis and is not periodic. It is not very numerous, and three or four individuals to the slide is the average. It may be found with either *F. nocturna*, *F. diurna*, or both; its habitat is the west coast of Africa. Recent investigations render it probable that a blunt-

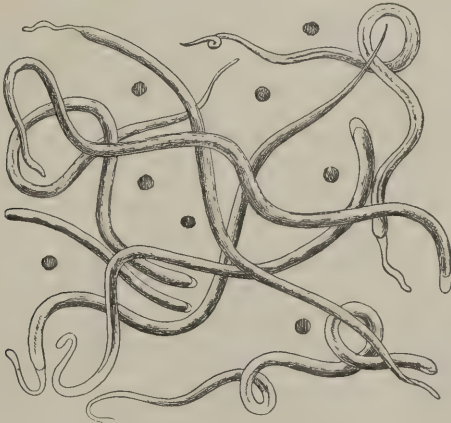


FIG. 132.—Embryos of filaria circulating in human blood. $\times 500$ (after Lewis).

tailed species from British Guiana is the parent form of this variety. If this be confirmed, *F. perstans* is endemic to both tropical America and Africa. Manson believes this worm is the cause of the "sleeping-sickness" or "negro lethargy." He thinks this is rendered probable by the fact that the organism has often been found in the blood in this disease.

Filaria Demarquaii has been found in the blood of negroes in the West Indies. The embryonal form, which alone is known, is smaller than *Filaria nocturna*.

Filaria volvulus inhabits the lymphatics of the subcutaneous tissue. The male is 30 to 35 mm. in length, the female 60 to 70 mm. The nodular swollen lymphatics form masses under the skin as large as a pigeon's egg, which increase in size with the growth of the parasite.

Filaria Magalhæsi was found in the heart's blood of a child in Brazil. It is thought possibly this may be the parent form of *Filaria Demarquaii*.

Filaria Ozzardi is found in British Guiana. *Filaria lentis* has been found several times in the crystalline lens. Several other species of *Filaria*

have been described—*F. conjunctivæ*, *F. restiformis*, *F. labialis*, *F. hominis oris*, etc.—but the limits of space forbid any detailed allusion.

Strongyloides Intestinalis (*Anguillula Stercoralis*, *Rhabdonema Intestinale*).—This parasite was discovered by Normand in the subjects of Cochinchina diarrhea. It occurs under two forms: the smaller, the one formerly called *Anguillula stercoralis*, is about 1 mm. in length, the anterior extremity being truncated, the posterior sharp; the larger (*R. intestinale*), of which the female alone is known, is 2.2 by 0.034 mm., similar in shape to the smaller form. The large form is always found in the intestine and gives origin to large parthenogenetic ova, which develop into male and female in water (alternate generation), and man becomes infested through drinking water containing the ova. When these are swallowed, the intestinal form (*Rhabdonema intestinale*) develops, and so on. The intestinal form lives in the mucus of the upper part of the small bowel, and is not now considered of any pathologic importance; its occurrence in severe tropical diarrhea is a coincidence.

ARTHROPODA (Insects, etc.).

This enormous group comprises the insects and other forms with jointed legs. Of the multitude of species composing it, but few are parasitic on man.

Linguatulida.—These are parasitic arthropods with a long round or flattened body composed of rings. The sexes are distinct and the head is furnished with hooks.

Linguatula Caprina (*Pentastoma Tænioides*, *P. Denticulatum*).—The larval form, *P. denticulatum*, is from 4 to 5 mm. in length by 1.5 mm. in width; the body is made up of 9 or 10 segments, the outer surface being covered with small spines; the mouth has four hooklets. It infests the herbivora; in man it has been found enclosed in a capsule in the spleen, liver, kidney, lung, and intestine. It is frequent in some countries, *e. g.*, Germany (30 times in 200 necropsies—Zenker; 5 in 47—Frerichs), but appears to have no pathologic importance. The adult form, *Pentastoma tænioides*, has a whitish lancet-shaped body, the male being from 15 to 17 mm. long, the female from 60 to 80 mm. The body is made up of 80 or 90 segments, covered with fine spines directed backward. It infests the nasal fossæ, frontal and maxillary sinuses of the dog and other carnivora. When the larval form in the rabbit or hare is eaten by a carnivorous animal, the larvæ make their way to the nose, become sexually mature, and cause epistaxis and sneezing, which scatters the eggs abroad; these fall in the herbage, are eaten by the rabbit, become encysted in the flesh, ready to undergo the same changes. Only one or two doubtful cases are on record of its occurrence in man.



FIG. 133.—*Linguatula caprina*
(larval form).

Porocephalus constrictus (*Pentastoma constrictum*) is only known in the larval state. It is much larger than the larval form of the preceding, being

from 10 to 13.5 mm. in length, with a white cylindric body, which has from 20 to 23 segments and two pairs of hooks; the surface is smooth. It is found coiled up in cavities in the liver and lungs, and is found free in the peritoneal cavity and in the intestinal canal. It has been seen several times in negroes, in Africa and elsewhere. The source of infection is unknown. It produces great irritation and apparently sometimes causes peritonitis.

Acarina (including *Mites and Ticks*).—*Demodex folliculorum* is found in the sebaceous glands, especially those of the face, also in the ceruminous and Meibomian glands. The male is 0.30 mm. in length, the female 0.36 to 0.40 mm.; the body is smooth, segmented, with four pairs of limbs and a proboscis. If numerous, it causes comedones and acne. The number in a normal gland is 1 or 2, in the comedones up to 15 or 20. These mites are found at all ages except in very young children.

Sarcoptes scabiei, a small parasite, the male 0.20 to 0.25 mm. in length, about one-third as large as the female, reddish gray in color. The itch-parasite lives in burrows in the skin, 0.5 to 3 mm. in length usually, sometimes much longer (Fig. 134); each burrow contains one female, which lives two or three months and lays one or two eggs each day. These are partly segmented when laid, and the young are hatched in less than a week. The burrowing of the female causes intense itching, and excoriations and eczematous eruptions are produced by scratching. Almost any part of the body may be attacked by the parasite, which is found throughout the globe.



FIG. 134.—Various aspects of the track of *Sarcoptes scabiei* (after Hardy).

Scabies is easily communicated, both by personal contact and by clothing. The itch-mites from other animals may infest man, usually only for a short period—from the cat, hog, horse, goat, and camel.

Among other mites are *Tyroglyphus siro*, the cheese-mite, occasionally found in the stools; *Glyciphagus domesticus*, the sugar-mite, causing "grocer's itch"; *Aeluroides farinæ*, the flour-mite, etc.

A great number of ticks attack man and animals; they suck the blood and cause intense itching, with skin-eruptions, sometimes suppuration and lymphangitis. Various species of *Ixodes*, *Trombidium*, and other genera occur as parasites.

Hemiptera.—In this group are several species which have become much degraded as a result of their long parasitic life. The lice are wingless bugs.

Pediculus Capitis.—The head-louse is exceedingly prolific; Leeuwenhoek calculated that an adult female will produce about 5000 eggs in two months. The nits hatch about the sixth or seventh day, and in three weeks' time the young are capable of reproduction. The color varies with the race of man; in the dark races they are always much darker than in the Caucasian. When transported from one race to another, they die in a short time. Head-lice are a frequent cause of enlarged cervical glands in children, which sometimes suppurate. *P. vestimenti* is probably the same species as the preceding. *P. pubis* is found principally in the white race. According to Moursou, the "tâches bleuâtres" are due to the bites of this species.

The discoloration appears about the punctures, stays a few days, and then disappears.

Diptera.—Before proceeding to the flies proper, the degenerated forms, the fleas, require a short notice.

Pulex irritans, the common flea, is found on man alone, but occasionally quits him for a short stay on the domestic animals. This species is found over the whole world.

Sarcophylla penetrans is the sand-flea or "chigger." The males and non-pregnant females are 1 mm. in length, and are only occasionally parasites seeking man to suck his blood. The impregnated female buries herself, head first, in the skin of man and animals. By the growth of the eggs the abdomen increases to an enormous size, and the skin over the animal becomes red, inflamed, and finally ulcerates. This species is common in tropical America, whence it has extended to West Africa and recently to South and East Africa. Sometimes 50 to 60 individuals are found in the body at once. It attacks the lower extremities by preference, and causes onychia, ulcers, and phlegmonous inflammations. The ulcers and cavities often lead to inoculation with tetanus.

Various species of *bot-flies* (*Oestrus*) are found under the skin, producing a swelling which becomes inflamed and from which the larva ultimately escapes or is extracted. In the Southern States and in South America, the screw-worm (*Lucilia macellaria*) commits great ravages. The eggs are laid in the nasal fossæ, maxillary and frontal sinuses, or the ears, especially of persons with ozena or otitis. The larva is provided with hooks at the anterior end, and the body has circles of spines, giving it the appearance of the thread on a screw (Fig. 135). This form destroys the mucous membrane, periosteum, and other soft parts, and even the bones. In 44 cases there were 30 deaths.



FIG. 135.—Larva of *Lucilia macellaria* (after Conel).
× 4.

Before leaving the subject, attention must be directed to the propagation of disease by insects, as maintained by Nuttall and others. As a result of experiments by various investigators, it is definitely proved in some cases, and rendered extremely probable in others, that various infectious diseases may be carried by insects, *e. g.*, Texas fever in cattle, anthrax, cholera, enteric fever, plague, tuberculosis, etc. In addition, the mosquito has been shown by a host of observers to be the chief agent in the propagation of malaria. The literature of the past few years contains numerous references to this subject. Animal as well as vegetable parasites are transported by insects.

PSEUDOPARASITISM.

A good example of this is furnished by Scheiber's case. A woman in Hungary, with nephritis, passed urine containing albumin, a little blood, and numerous minute worms. These were present by thousands daily, and proved to be *Rhabditis pellio*, a species inhabiting damp earth and putrefying organic substances. On investigation it was found that the Hungarian peasants make use of earth poultices to relieve pain. The patient had applied earth to the thigh, whence the worms had entered the vagina and

multiplied. Hysterical individuals frequently pretend to pass earthworms and similar objects. Among other pseudoparasites are substances found in the urine or feces, which were in the vessel originally and did not come from the body at all. Blood-clots or strings of mucus evacuated with the urine are frequently mistaken for worms, as are shreds of membranes, vegetable tissues, or partly digested flesh in the stools.

The condition known as myiasis is due to swallowing the eggs of flies, in food or otherwise. The larvæ develop in the intestine and are discharged from the bowels. The flower-fly (*Anthomyia canicularis*) is one of the most common species, sometimes two or more liters of the larvæ being passed by a single patient. More than fifteen species are known to infest man. They give rise in some cases to colicky pains and diarrhea; in others no inconvenience is experienced. Blanchard¹ has collected 35 cases of pseudo-parasitism of some 10 different species of the common "thousand-legs"; 27 cases were in the nasal fossæ and neighboring cavities and 8 in the alimentary canal.

¹ *Arch. de Parasit.*, i., 452, 1898.

INTOXICATIONS.

INTRODUCTION.

Definition.—A poison is a substance of definite chemical composition, which by virtue of its constitution is capable, when brought in contact with the tissues of the body, of modifying the cellular activity of one or more organs to such an extent as to impair health or destroy life. This definition excludes all substances which cause injurious effects on account of their physical properties. Powdered glass taken into the stomach might cause death, and yet it would not properly be called a poison, since the resulting injury is due to the physical properties and not to the chemical constitution of the glass. Life may be destroyed by burns from hot air, water, or metal; and yet in such a case the air, water, or metal could not be considered a poison, because the ill effects are due to the temperature of these substances. This definition excludes bacteria and animal parasites. These may elaborate bodies that are harmful by virtue of their chemical composition, and they may contain such substances within themselves, but the bacterial cell cannot be regarded as a chemical compound.

Sources of Poisons.—Poisons may be grouped according to the sources from which they come, as follows:

Mineral: as arsenic, lead, phosphorus, etc. Many substances derived from the mineral world owe their poisonous properties to certain artificial changes to which they have been subjected. Silver, as it is found in nature, is inert; but in the form of the nitrate it becomes quite active. While some of the phosphates and phosphites are injurious to the body when employed in large doses, their action is hardly comparable with that of the isolated phosphorus, in which form this element does not occur in nature.

Synthetic: as anilin, nitroglycerin, antifebrin, etc. The discoveries of the synthetic chemist have demonstrated the fact, long denied, that the toxicologic action of a substance is determined by its chemical composition. Indeed, we are now able to predict within certain limits the physiologic action of a compound from a knowledge of its chemical structure, and this action can be modified by the substitution of one group of atoms for another. The possibility of thus building up new substances capable of inducing modified or even radically different effects seems to be unlimited, and this branch of chemistry is still quite new. Additional discoveries along this line will probably greatly advance our knowledge of the science of toxicology.

Vegetable: as morphin, strychnin, abrin, ricin, etc. These are chemical compounds that result from the activity of plant-cells. Poisons originating in this way are capable of many subdivisions on the basis of their chemical composition. We have the vegetable alkaloids, the poisonous acids of vegetable origin, as oxalic acid, and the poisonous glucosids and vegetable albumins.

Bacterial: as tetanin, the diphtheria toxin, and other bacterial toxins. These again are capable of subdivision, as the basic poisonous bacterial products, or the ptomaines, and the so-called toxalbumins. In reality the bacterial poisons belong to the foregoing group, inasmuch as bacteria are vegetable organisms.

Animal: as the venom of serpents, the poisonous secretions of certain fishes, the poisonous leukomains, etc. These also may be subdivided. Some of them are not poisonous to the animal in the body of which they are generated, but act as poisons upon the tissues of other animals; while others act injuriously when allowed to accumulate unduly in the organism in which they originate.¹

MINERAL POISONS.

Arsenic.—To the cells of the higher animals, arsenic is a universal poison. So far as we know, there is no vertebrate immune to its action, although susceptibility varies within wide limits. Not only are all of the higher animals susceptible to arsenic, but it is poisonous to all kinds of tissues. It produces deleterious effects when applied to the unbroken skin, when it comes in contact with mucous surfaces, when administered subcutaneously or by mouth, and when inhaled in the gaseous form. When applied locally in sufficient quantity, it causes necrosis of tissue. It may alter the composition of the blood, cause atrophy of the muscles, modify the growth of bone, and induce pathologic changes in the nerves. Loew found that algae and certain infusoria grow in neutral solutions containing 1 part of arsenic to 1000 of water. He concludes from his experiments that, to the lowest forms of animal life and to many of the lower plants, arsenic is not a poison. Arsenous acid may kill the lower forms of life; but it does so by virtue of its acid reaction, and not on account of its arsenic content.

Authorities are not altogether in harmony concerning the *modus operandi* of this poison. It is generally believed that it induces cellular death by its direct local effect as an irritant. Its corrosive action has been attributed to the supposed avidity with which it is said to combine with albumin; but Binz and Schulz claim that there is no albuminate of arsenic, and that it has, properly speaking, no corrosive action. These authorities teach that the poisonous action of arsenic is due to the readiness with which it gives off and takes up oxygen. Arsenous acid is a reducing agent, while the *arsenic* compound is equally effective in causing oxidation. They show that various animal and vegetable substances, at body-temperature, reduce arsenic acid to arsenous acid and oxidize the latter to the former. Both of these processes are quickly wrought, both within and without the body. The sudden and continued withdrawal of oxygen from one molecule and its transference to another are believed by Binz to be the true explanation of both the therapeutic and toxic action of arsenic. Binz states that the most important lesions induced by arsenic are found in those tissues which are specially endowed with the function of receiving and utilizing the oxygen of the blood, such as the glandular

¹ It is impossible, in a work on general pathology, to discuss all poisons. The writer has therefore selected a few of the most important. Moreover, he has confined himself to a description of the pathologic changes induced in the body by these substances. He has not lost sight of the fact that this is a chapter in a work on pathology. The chemistry of poisons and the symptoms induced by them have been omitted, so far as possible, as not being in place in a work of this kind.

protoplasm. A parallel to this is believed to exist in the action of certain oxids of nitrogen. NO is said to be poisonous because it takes up oxygen, and NO₂ is poisonous because it gives off oxygen. A more interesting example of this kind of action is shown in the preparation of anilin black. Anilin chlorid and potassium chlorate are mixed; but no change takes place until a small bit of ammonium vanadate is dropped into the mixture, when all of the anilin is changed into anilin black. The vanadium compound takes oxygen from the chlorate and transfers it to the anilin. One part of the vanadate may in this way produce 20,000 parts of anilin black. This interesting theory of the action of arsenic may be designated as the theory of "the oscillatory molecule of oxygen."

It has been held, especially by certain French writers, that arsenic owes much of its poisonous action, if not all, to its effect upon nervous tissue, in which it has been believed to replace phosphorus. This theory is founded upon the belief that arsenic is deposited in large amount in the brain, which is certainly erroneous. Many investigators have shown that the amount of arsenic in the brain, after poisoning with this substance, is much smaller than that found in the liver and kidneys. In 1884 the writer found this to be true, both in acute and chronic poisoning with white arsenic, and in acute poisoning with the more soluble preparations.

Chronic arsenic poisoning is frequently accompanied by the development of some lesion of the skin. Arsenic rashes, generally accompanied by itching, are for the most part of the erythematous type; but papules, vesicles, pustules, ulcers, and gangrene have been reported. The long-continued therapeutic administration of arsenic is sometimes followed by a pigmentation of the skin, which is generally most marked over the upper covered portions of the body, but may extend to the hands and face. The effects of arsenic on the skin have led to the supposition that this poison is eliminated through the skin; and Brouardel and Pouchet have detected arsenic in the skin, nails, and hair of persons poisoned with it. Rarely there is observed a form of cutaneous pigmentation known as arsenic melanosis. This is due to the deposition of a nonarsenic decomposition-product of hemoglobin in the skin. The skin becomes dark brown; and this special coloration is most marked, as a rule, over the neck and extremities, although it has been observed in the axillæ and popliteal spaces. Microscopic examination shows reddish, brownish, or black granules about the lymph-vessels of the papillæ. In very rare instances this pigment is deposited so abundantly that it forms small tumors. Chemically this coloring matter is identical with the bilirubin of the bile and with the hematoidin crystals found in various parts of the body where there have been extravasations of blood.

While poisonous doses of every form of arsenic have more or less destructive action on the coloring matter of the blood, this effect is most marked when the poison is inhaled in the form of the arsenid of hydrogen. The urine becomes dark red and even black, from the rapid disintegration of the red corpuscles. Formed elements in the urine, such as epithelial cells and spermatozoa, may be stained brownish red or yellow. The broken-down hemoglobin is converted into bile-pigment so rapidly that icterus is soon observable, and after twenty-four hours the skin may be quite thoroughly bronzed. Stadelmann studied the action of this poison on dogs with biliary fistulæ, and found that the amount of bilirubin was increased twenty times.

The nervous system is markedly susceptible to the action of arsenic. Arsenic paralysis may result from either acute or chronic poisoning, and from internal administration or external application. There may be no evidence of it after large doses, and it may result from relatively small quantities. Why it appears in some cases of arsenic poisoning and not in others has never been satisfactorily explained. Jaccoud thought it most common in alcoholics, but this has been denied by others. The paralytic affections vary in intensity from slight weakness to complete loss of motion. They may be transitory or permanent. They set in with the first symptoms of gastric irritation or may be tardy, first appearing weeks after other symptoms have manifested themselves. Disturbances of motion are generally confined to the extremities, but there are some cases reported in which the muscles of the trunk have been involved. The four extremities are affected in most instances, but the legs are more frequently involved than the arms. Sometimes there is hemiplegia, but more often the paralysis is symmetric. The paralysis is most marked in the distal parts, the fingers and toes, growing less evident nearer the trunk. Paralysis is always associated with muscular atrophy, which is characterized by its early appearance and rapid development. The atrophy may be degenerative or simple. Diminished response to both faradic and galvanic stimulation is observed.

The marked atrophy of the muscles of the extremities gives to the patient a peculiar appearance. Especially in cases following acute arsenic poisoning, it happens that the face and trunk appear perfectly healthy, while the limbs are shrunk, the subcutaneous fat on them has disappeared, and the nails are diseased or have fallen out. The skin of the extremities is withered and dry, except over the hands and feet, which are often bathed with cold perspiration. Sometimes there are ulcers. Edema is rarely observed. The tendon reflex is absent in all cases; the skin reflex has not been well studied. In some cases there are contractures, especially of the knee-joint. These are due to unequal involvement of individual groups of muscles. Disturbances of sensation accompany those of motion, and sometimes the former predominate. Pain is rarely absent; in many cases it becomes the most distressing symptom.

The histologic changes which accompany these abnormalities of motion and sensation have not been closely studied. It was formerly believed that arsenic induces a myelitis. The theory that arsenic replaces the phosphorus in nervous tissue has already been referred to, and has been found to rest upon insufficient evidence. Popoff concluded from his experiments upon animals that arsenic induces a central myelitis and that the peripheral nerves remain unaffected; but more recent studies show that the changes occur in the nerves and that arsenic polyneuritis does not differ from that induced by other toxic agents. There are proliferative changes in the neurilemma-cells, and the inflammation may be exudative. Regeneration may occur, as it does after experimental division of nerves.

Cases of paralysis of nerves not usually involved are known. Such are the instances of *anaphrodisia arsenicalis* reported by Biett and later by Charcot, also of paralysis of the vocal cords observed by Mackenzie.

The brain and cord do not always escape the direct action of arsenic. This is shown both by the symptoms and postmortem findings. In rare instances cerebral hemorrhage has been observed; but usually in the most acute cases hyperemia of the meninges and effusion into the ventricles are the only pathologic changes found in the brain, and these are not constant.

Mummification of the body after death from arsenic poisoning has been frequently observed, and has been regarded by some as valuable evidence concerning the cause of death in cases which have been investigated legally. At least one instance of this kind attracted much attention some years ago, largely because Robert Koch figured as an expert in it. The body was exhumed after the coffin had lain partly in water for eleven months. Traces of arsenic were found in the body, which was markedly mummified. Koch considered the mummification strong evidence in favor of death from arsenic. It was shown that tartrate of antimony containing traces of arsenic had been administered medicinally, and this was supposed to account for the small quantities of arsenic found in the body. Although the accused was found guilty, toxicologists have not agreed concerning the evidence. Arsenic is

generally regarded as a powerful antiseptic, and unfortunately it is a common ingredient of embalming fluids.¹ However, its antiseptic properties have been greatly overestimated, and many bacteria grow abundantly in media which contain much more arsenic than that found in persons poisoned with it. Indeed, in some instances of known arsenic poisoning, the liver and spleen have been found to be unusually soft and yet rich in arsenic. The writer ascertained, in carrying on some toxicologic investigations a few years ago, not only that some germs grow abundantly in the presence of large quantities of arsenic, but that all of the arsenic may be converted into gaseous compounds and given off, leaving the mass of tissue wholly free from arsenic. Too much importance must not be given to mummification as an evidence of arsenic poisoning. Mummification is by no means always due to arsenic, nor are arsenic bodies always well preserved. The vomiting and diarrhea, which are persistent and profuse in most cases of arsenic poisoning, not only empty the alimentary canal, but also materially reduce the water in the body; and to these effects, rather than to the arsenic, is to be attributed the delay in putrefactive changes frequently observed after death from arsenic.

At the autopsy held soon after death from arsenic, the skin is generally cyanotic; and the body may be much reduced in flesh, even in cases of acute poisoning. The mucous membrane of the mouth, pharynx, and esophagus shows no abnormality. In a large percentage of the cases, gastritis is more or less marked. Although the greater part or even the whole of the mucous membrane may be reddened, almost invariably there are areas in which the involvement is deeper than elsewhere. The erosion varies greatly in intensity. It may be confined to the mucous membrane, or it may penetrate all the coats of the stomach and cause perforation. As long ago as 1753, Spreegel showed that these gastric lesions result not only when arsenic is taken by the mouth, but also when it is absorbed from wounds; and since that time they have been frequently induced experimentally in the lower animals by the hypodermic administration of neutral solutions of arsenic. The pathogenesis of the gastric lesions has been a matter of some dispute among toxicologists. It has been generally assumed that the erosions are due to the local action of the poison; but in view of the fact that they are produced by the absorption of arsenic when applied to raw surfaces and follow hypodermic administration, Taylor and others have claimed that arsenic gastritis (and enteritis as well) is a specific effect of arsenic poisoning and is not due to local action. Virchow very properly states that the gastritis of arsenic poisoning cannot be considered specific, for the same condition with cloudy swelling and a tendency to fatty degeneration in the glandular cells of the stomach is observed not only after poisoning with arsenic, antimony, or phosphorus, but also as a result of certain infectious diseases, such as variola. However, this does not explain anything. It only gives a wider interest to the study of the pathogenesis of toxic gastritis. To say that the poison of variola induces in the stomach lesions similar to or identical with those induced by arsenic cannot be accepted as a satisfactory explanation of how the poison in either case causes these pathologic changes. Moreover, it is altogether possible that the mode of action of the two poisons may be unlike, notwithstanding the fact that identical results are reached.

Binz and Schulz have endeavored to explain the gastric lesions in accord

¹ Recently formaldehyd has been substituted for arsenic by many embalmers.

with their theory of the action of arsenic, which has been referred to above. They hold that in the alimentary canal there are certain "predilection" places in which the poisonous action of arsenic is most marked, and that the peptic glands constitute one of these places.

Böhm has suggested that the arsenic lesions of the stomach may be due to partial paralysis of the blood-vessels of this organ. Hermann thinks it possible that arsenic may affect the peripheral nerves of the stomach, and thus indirectly so influence the local blood-supply as to lead to inflammatory changes and even to hemorrhagic erosions.

Filehne found in some experiments upon rabbits that the gastric erosions do occur when the contents of the stomach are kept neutral or alkaline, and he concludes from this that the lesions are due to self-digestion of the walls of the stomach; but he fails to explain how the arsenic makes self-digestion possible.

Of course, when applied in mass to the mucous membrane, arsenic has a locally destructive action. Hoffmann's case illustrates this nicely. He found a putty-like mass of arsenic in the stomach, and, directly under it and of the same size and shape, an erosion. It is also true that arsenic administered hypodermically is eliminated by the mucous membrane; but it is difficult to believe that, when thus given, it can accumulate in sufficient quantity in certain small areas to cause severe erosions. It will be seen, therefore, that the pathogenesis of the gastric lesions of arsenic poisoning must be left without satisfactory explanation for the present.

In cases where a large amount of white arsenic has been given by the mouth, close inspection—especially examination with a magnifying glass—may reveal undissolved particles of the poison. When the examination is made some days after death, yellow spots may sometimes be found in the stomach or large intestine, or in both. That these colorations are due to the sulphid of arsenic has been affirmed by some and denied by others. In several instances the writer has by analysis detected arsenic in these yellow spots. Brown and Davies examined similar stains in the stomach and intestines, and found only traces of arsenic. They conclude that the coloration was due to some decomposition-product of bile-pigment. However, the evidence adduced for this conclusion might be criticised. Frequently the wall of the stomach or intestine is stained through, so that the coloration may be seen on both the mucous and serous surfaces.

Hoffmann has shown that the sulphid of arsenic may be formed in the body as early after death as two days. He points out the fact that knowledge of the possibility of the formation of this compound so soon may be of great importance, since realgar or orpiment may be employed in suicide, but neither would likely be used with murderous intent. His experiments enable him to state positively that the finding of the sulphid in the alimentary canal two days (or longer) after death is no proof that the arsenic was taken in this form.

The mucous membrane may be thickened with cloudy swelling. At certain points the mucous membrane may be stained with blood, and on attempting to wash away these stains it will be found that it has been detached from the subjacent tissue and is also removed. In some instances deep necrotic changes may be observed. Even when macroscopic lesions are not detectable, there is an infiltration of the tissue with round cells, a condition which has been designated by Virchow as *gastro-adenitis arseni-*

calis parenchymatosa. The upper portion of the small intestines may show alterations similar to those observed in the stomach. Multiple ecchymoses may be found along the intestinal tract. The contents of the small intestine are often thin, watery, and similar to the rice-water stools of cholera. The solitary follicles and Peyer's patches are markedly infiltrated. The alterations in the large intestine may be slight or more apparent. Frequently the epithelial layer is removed from areas more or less extensive, and the mucous membrane is infiltrated with white blood-corpuscles. In animals the above-mentioned changes in the alimentary canal may be observed, according to Pistorius, within two or three hours after subcutaneous administration and within forty minutes after intravenous injection.

The changes induced in the liver and kidneys by arsenic are for the most part microscopic. Only in exceptional instances has fatty degeneration progressed so extensively that it can be recognized by the unaided eye. Ziegler and Obolonsky have made a close histologic study of these organs, and the following statements indicate their findings. Fatty change of the liver-cells is never absent, and is characterized by the presence of small drops in the protoplasm. The fatty changes, however, never involve any large portion of the cells. There are exceptions to this statement, and in some cases the change is as marked as it is in phosphorus poisoning. In many instances this is the only detectable alteration. In others there may be cloudy swelling and necrosis of individual cells. The nuclei often stain imperfectly or fail wholly to do so. Granules staining with safranin may be seen in the protoplasm, showing that the nuclei have been broken down. Sometimes individual cells are seen to be shrunken and homogeneous, appearing brown in stained preparations and showing colored granules instead of nuclei.

That the cells involved in some of these changes are still capable of multiplication is shown by the observation of typical karyokinetic figures. It may be remarked in this connection, that, in the examination of the livers of rabbits long under the influence of arsenic, one gets the impression that the number of double nuclear cells is greater than normal. These proliferating cells may be observed in different parts of the acini, and it cannot be said that they have any local relation to the necrotic foci.

Most of the Kupffer cells are filled with fat drops, and in poisoning of short duration fatty changes are often more advanced in these than in the other cells. Fatty changes in the intra-acinous capillaries are seen here and there. These were first observed in animals which had been treated with arsenic for two days, but the best examples were found after from eleven to seventeen days.

As proliferative phenomena, there were observed swelling of the endothelial nuclei, increase of chromatin, and the appearance of typical karyokinetic figures. The proliferating cells are sometimes round; sometimes they put forth processes which cross the lumen and attach themselves to the opposite wall of the capillary.

The periportal connective tissue is often found to be in a state of proliferation, which is indicated partly by the presence of more or less abundant karyokinetic figures, partly by the increase of cellular elements, and by the presence of numerous cells with large nuclei and rich in protoplasm. These changes can be seen in animals which have been only two days under the influence of the poison, but they become more marked after two or three

weeks. However, one must not expect to find them developed to the same degree in all animals.

In the epithelium of the bile-ducts there is a multiplication of the epithelial cells simultaneously with the proliferation of the connective tissue. After poisoning of long duration, there often appears to be a formation of new bile-ducts. However, the number of bile-ducts in the periportal connective tissue in rabbits is normally so great that a positive statement on this point cannot be made.

Changes strictly attributable to an inflammatory condition are not prominent. However, single leukocytes are observed in the proliferating areas, and sometimes the intra-acinous capillaries contain many leukocytes. In point of time or place, the proliferation shows no recognizable dependence upon the degeneration.

In dogs which have been treated for three months with doses of from 0.01 to 0.1 gm., extensive fatty degeneration is observable. Some liver-cells show vacuoles. Furthermore, many endothelial and connective-tissue nuclei are filled with granules, which stain intensely red with safranin. In the kidneys the epithelium of the tubuli recti are fatty to a high degree.

In acute arsenic poisoning, hemorrhagic points may be found not only in the alimentary canal, as has been stated, but also in the muscles, pancreas, the lungs, in serous membranes, and in the endocardium. The presence of ecchymoses in the endocardium of the left ventricle is frequently observed and is regarded by some as pathognomonic of arsenic poisoning.

In chronic arsenic poisoning, fatty changes may be observed not only in the organs mentioned, but also in the muscles, including those of the heart and diaphragm, and in the mesenteric glands.

Antimony.—The pathologic changes induced by preparations of antimony are so similar to those caused by arsenic that no extended statement is necessary. Indeed, the remarks on the pathologic anatomy of antimonial poisoning will be largely confined to the few lesions which are distinguishable from those of arsenic poisoning.

The frequency with which the tartrate of antimony is employed as a mordant has given opportunity for the study of its effects upon the unbroken skin. A pustular eczema is induced, and the suppurative process may extend through the deeper layers of the skin and even involve the subjacent tissue. Moreover, these breaks in the continuity of the cutis expose the tissue to the action of pyogenic germs, and the extension of the lesions may be due to these.

Upon the mucous membrane of the alimentary canal, the action of antimony differs from that of arsenic most notably in the appearance of aphthous patches in the mouth, esophagus, and stomach. Indeed, the local effect of arsenic is less marked than that of antimony. Schmiedeberg accounts for this on the ground that preparations of arsenic are absorbed more readily than those of antimony. It is on account of its marked local irritation of the stomach that antimony, acting reflexly, becomes the powerful emetic that it is.

The lesions produced in other organs by antimony are practically identical with those induced by arsenic.

Phosphorus.—Poisoning with phosphorus is so frequent, and the lesions induced by it are so well marked, that it is a favorite study of pathologists.

In doses of 0.1 gm., phosphorus is poisonous, inducing gastritis accompanied by vomiting and pain. Death may result within a few days, from failure of the heart; but more frequently the primary symptoms subside and are followed by a short period of comfort, when secondary symptoms manifest themselves. Pain reasserts itself; the liver is found to be perceptibly enlarged; icterus is observed; there may be some elevation of temperature; vomiting is renewed; the pulse becomes feeble; and delirium, frequently accompanied by convulsions and terminating in a coma resembling that of uremia, may mark the last stages of the intoxication. Often ecchymoses appear beneath the epidermis, and hemorrhages from the nose, stomach, bowels, and uterus have been noted. As a rule, death occurs in acute poisoning after from five to fifteen days.

Fatty changes are found in the most diverse tissues, such as the epithelium and glands of the stomach and intestines, the liver, kidneys, pancreas, lungs, heart, blood-vessels, and both smooth and striated muscles. Ecchymoses, and occasionally profuse hemorrhages, may be found in different tissues. When the poison has been taken by the mouth, erosions are frequently seen in the stomach and upper intestines, and the mesenteric glands are hyperemic and swollen. Fatty changes in the liver are easily detectable in experimental animals as early as twelve hours after the administration of the poison, and in chronic poisoning many liver-cells will be found to be wholly destroyed. In chronic poisoning, both the heart and the kidney may suffer most extensive fatty changes.

Wegner treated animals with gradually augmented doses of phosphorus, and states his findings substantially as follows: The liver-cells of the periphery are destroyed by fatty changes. In the greater number of the acini the cells are stained with bile, and this is due to the pressure of proliferating tissue on the minute branches of the gall-ducts. Soon an interstitial hepatitis will be found. This invariably leads to atrophy, of which three kinds have been observed. These are (1) a smooth induration of the organ, (2) a lobulated liver with many deformities, (3) a typical granular atrophy, the classic cirrhosis of the liver. In all of these there is chronic icterus. When the last-mentioned form of atrophy exists, it is found to be accompanied by secondary lesions well known in human pathology—venous hyperemia of the mucous membrane of the stomach and intestines and indurative enlargement of the spleen. These animals develop ascites and hydrothorax.

Hemorrhages and ulcerations were found in the stomach. In the animals kept for months under the influence of the poison, the mucous membrane of the stomach was found to be thickened to two or three times the normal condition, indurated, and colored gray or brown. In growing animals, small doses long continued produced sclerotic bone in the endochondral zones, and the periosteal deposition became at the same time thicker. In adult chickens, small doses caused the medullary cavities to fill with bone, and in case of fracture the formation of callus was hastened. When administered in small doses to pregnant animals, phosphorus is believed to increase the formation of bone in the fetus.

In a dog killed after it had been given small doses of phosphorus daily for thirty-six days, Krönig found necrobiotic changes with fatty degeneration in the liver-cells, accompanied by dilatation of the blood-vessels and the gall-ducts. In another animal which died after seventy-nine days, he found a hyaline degeneration in the walls of the blood-vessels and the usually observed changes in the liver-cells. In a third dog killed after one hundred and six days, the changes in the liver-cells were much more pronounced. Many appeared

homogeneous or contained vacuoles and were without nuclei or showed only broken-down nuclei. The lobules contained brownish foci consisting of granules, leukocytes, and disintegrated cells. Swelling and hyaline degeneration of the endothelium of the blood-vessels were noticed. The periportal connective tissue was increased. The blood-corpuseles were believed to have suffered hyaline degeneration and to be deprived of the power of normally performing their physiologic function.

Ziegler and Obolensky observed, in the early stages of phosphorus intoxication, fatty and other changes in the liver-cells. The nuclei were often found to be broken down, while granules stained with safranin could be seen distributed through the protoplasm. Even after more chronic poisoning, the amount of fat in the liver-cells was often found to be small. The degenerative changes were generally found to occur simultaneously in different parts of the acini, but in some instances they were most marked along the periphery.

The question has arisen as to whether the fat found in the liver and other tissues is formed *in situ* or results from an infiltration. Lebedeff has endeavored to prove that this fat is transported from subcutaneous deposits. He fed dogs for a long time upon foreign fats, such as linseed oil, and, after he supposed that the normal fat of the body had been replaced by that of the food, he poisoned the animals with phosphorus and satisfied himself that the fat found in the liver-cells was of foreign origin. However, there is no proof that the subcutaneous fat was replaced by that of the food. Leo claims that both processes go on. He finds experimentally that, while other parts of the body may lose and the liver gain in fat, the total amount in the body is increased by phosphorus poisoning, and consequently he concludes that there must be some actual production. The location of fatty globules in the liver-cells, in the glands, and in certain muscles, its speedy appearance after the administration of the poison, and the other evidences of cellular degeneration leave little room to doubt that the fat is at least in part formed *in situ*. No proof has, however, been brought, according to Rosenfeld, Taylor, and others, that the fat is formed out of the proteids of the cells.

One of the most interesting lesions of chronic phosphorus poisoning is the necrosis of the bones of the jaws formerly observed frequently among workers in match-factories. This necrosis is due to the action of vapor of phosphorus, and occurs among those who dip the ends of the matches in the phosphorus bath. It begins as a periostitis, most frequently in the inferior maxillary, about a decayed tooth. It is accompanied by salivation and great pain. Extraction of the tooth shows the presence of pus in the alveolus. The suppuration extends into the alveolar processes, destroys the gum, and involves the adjoining teeth, which become loose and fall out. The pus formed gives off a fetid phosphorus odor. The destructive process may not stop with the gum, but may involve the skin; and deep abscess may form in the neck. Early in the process there is an abnormal deposition of osseous tissue; but later this is destroyed, and the old bone forms a sequestrum which must be removed. Amyloid degeneration of the abdominal organs is one of the secondary effects of the long-continued suppuration, and basilar meningitis frequently leads to death. Improved methods in the manufacture of matches and advanced sanitation in the factories have greatly diminished the number of cases of phosphorus necrosis.

Tissue metabolism is much disturbed in poisoning with phosphorus. This cannot be explained on the supposition that any large proportion of the

oxygen needed to carry on normal metabolism is consumed in the oxidation of the phosphorus, because but little oxygen is required to oxidize the small amount of phosphorus which constitutes a fatal dose, and secondly because it has been demonstrated that no appreciable oxidation of phosphorus takes place in the body. Bauer has shown that the amounts of oxygen taken into the blood and of carbonic acid given off are enormously decreased in phosphorus poisoning. According to this observer, not only is fat formed from proteid constituents of the body, but paralactic acid occurs in the blood and urine in abnormal quantity, and much of the nitrogen which normally exists in the form of urea is eliminated in the urine as ammonia. The red blood-corpuscles rapidly decrease in number, and the conversion of hemoglobin into bile-pigment takes place so rapidly that not only is the whole body icteric, but the urine is highly colored with this pigment. That the blood-corpuscles disintegrate more rapidly than their coloring matter can be changed into bile-pigment is shown by the presence of unchanged blood-pigment in the urine. According to the researches of Selmi, unknown poisonous basic substances appear in the renal secretion. These have been designated as phosphorus ptomains. The urine contains ammonia, paralactic acid, albumin, pepton, bile-pigments, bile-acids, hemoglobin, bases containing phosphorus, fat globules, fatty casts, cell detritus, and blood-corpuscles. Whether or not leucin and tyrosin exist preformed in the urine is a question not yet satisfactorily settled. At any rate, these crystalline bodies may be obtained by the usual method of concentrating the urine and extracting with alcohol.

The suggestion that acute yellow atrophy of the liver is a form of phosphorus auto-intoxication resulting from the formation of free phosphorus in the intestines by the reducing action of bacteria on phosphates rests upon no scientific basis.

The Oxygen Compounds of Phosphorus.—Schulz has studied the action of salts containing the oxygen compounds of phosphorus. The hypophosphite of soda is inert. The phosphite of soda is markedly poisonous, having its chief effects on the central nervous system and on the glandular organs of the abdomen. After acute poisoning the mucous membrane of the fundus of the stomach shows large blood-extravasations, while the pylorus is dotted with multiple ecchymoses. In more chronic cases the liver and kidneys show a fatty degeneration. After death from phosphite of soda subcutaneously administered, the intestinal tract is highly inflamed, the glands especially being involved. The mucous membrane is infiltrated with blood and shows numerous hemorrhagic points. The pyrophosphate causes gastric and intestinal hemorrhage, and hemorrhagic spots under the renal capsule have been observed. The metaphosphate also acts as a gastro-intestinal irritant.

Lead.—Lead combines readily with albumin, and some of the lesions found in the alimentary canal after poisoning with this substance may be due in part to this action; but that lead is a poison merely on account of the readiness with which it forms a compound with albumin is not true, because the albuminate of lead and other noncorrosive compounds of this metal are quite as poisonous as the inorganic salts.

In acute lead poisoning, gastritis is generally more or less marked. There may be ulceration. The mucous membrane of the intestines is shrivelled, anemic, and frequently stained grayish brown with the sulphid of lead. In animals, serous effusions under the membranes of the brain and cord have

been observed. Coen found inflammatory infiltrations in the lungs, liver, and kidneys, with cloudy swelling and vacuolization in the epithelium of the stomach, intestines, pancreas, kidney, adrenals, and liver, but no evidence of fatty changes.

Chronic lead poisoning furnishes the pathologist with abundant material for study, inasmuch as the lesions are both decided in degree and extensive in area.

Disturbances in the alimentary canal occur both when the poison enters by the mouth and when administered hypodermically. Indeed, when soluble salts are injected under the skin or intravenously, they are in part eliminated from the circulation into the stomach and intestines. Coloration of the gums is one of the signs of chronic saturnism first looked for by the physician. Massazza observed it in dogs three days after the administration of the poison was begun, but generally it appears much later. This coloration is due to the formation of the sulphid of lead. The gums and often the teeth are stained; sometimes the inside of the lips and cheeks shows flame-like bluish patches. This sign is most marked in persons who neglect cleansing the mouth. Ulceration of the stomach and upper intestines is sometimes found. The peptic glands undergo fatty degeneration and may be obliterated in certain areas. The submucosa is thickened on account of a proliferation in its connective tissue. The solitary and agminated glands of the intestines suffer fatty degeneration or atrophy. Fatty changes may be detected in the muscular walls of the stomach and intestines. There may be contractions in the connective tissue of the walls of the alimentary canal, leading to abnormalities of form and position.

Lead colic with great pain may occur repeatedly in the course of chronic poisoning, and even for months, possibly years, after the introduction of the poison into the body has ceased. This colic is accompanied by contraction of the circular fibers of the intestines. If the contractions are slight and interrupted, there will be diarrhea; but when they are complete and continuous, a most intractable constipation results. Lead colic was formerly believed to be due to an affection of the sympathetic system, especially of the solar plexus; but recently it has been attributed to irritation of motor ganglia in the intestinal walls. Strangury or ischuria may occur along with lead colic. The blood-pressure is decidedly increased during the colicky attack.

After death from an attack of colic in a man who had long suffered from chronic lead poisoning, the writer found the intestines so tightly constricted for a distance of several inches that neither air nor water could be forced through them. However, too much importance must not be attached to this condition, as it may be observed after death from other causes. In chronic lead poisoning experimentally induced in rabbits, the cells of the peptic glands are found to be cloudy and undergoing fatty degeneration, and the signs of venous stasis and ecchymosis are present. There is proliferation of the submucous connective tissue, and sclerosis may be well marked.

It is generally believed that lead is eliminated to some extent by the skin. Cases of chronic poisoning have been reported in which the epidermis has been darkened on the application of dilute solution of sulphid of sodium or after bathing in water impregnated with hydrogen sulphid gas. However, perspiration collected after the administration of pilocarpin in these cases has been found free from lead. Kobert suggests that the poison may be contained in the epidermis in an insoluble form. Lesions of the skin are not constant in this affection, but may occur; the most common form is a pustular erythema. The existence of an *icterus saturninus* has been both affirmed and denied by

good clinicians, which shows that it may occur, but is not constant. In long-continued saturnism the subcutaneous fat disappears, the skin becomes wrinkled, dry, and brown, giving an appearance of old age. Anesthesia is occasionally observed over circumscribed areas, and may be confined to the skin or extend to deeper tissues; it is due to the action of the poison on peripheral sensory nerves and is transitory.

The number of red corpuscles and the amount of hemoglobin are diminished. According to Grawitz, the red blood-corpuscles in lead poisoning often contain basophilic granules, staining with methylene-blue.

The disturbances of vision which occur in chronic saturnism are probably secondary to the effects of the poison on the kidneys. Stood divides them into two classes: the first he considers a neuritis due specifically to the action of lead, and states that it may occur without the co-existence of albuminuria; the second he regards as a retinitis such as may occur with contracted kidney due to other causes. Between and connecting these is hydrops of the sheath of the optic nerve, which may be a consequence either of nephritis with hypertrophy of the left ventricle or of peripheral retrolubar neuritis. The neuritis generally begins with inflammatory phenomena, easily recognizable with the aid of the ophthalmoscope; but it is often impossible to determine exactly what part of the nerve is most seriously affected. According to Oeller, hyaline deposits in the vessels of the choroid and retina may be found in some cases of lead poisoning.

The minute anatomy of the contracted kidney of chronic lead poisoning has been studied by numerous clinicians and pathologists, but their findings have led to diverse views. In brief, it may be said that some contend that the lesions begin in the blood-vessels. The arteritis, they say, leads to contraction here and there and to occlusion of the lumen of the blood-vessels, while the parenchyma secondarily becomes atrophied and the interstitial connective tissue proliferates more or less. Others hold that lead first injures the secreting elements, and that the affection of the blood-vessels is secondary and in no wise characteristic. Guyler believes that the primary and most important histologic changes are found in the blood-vessels and begin in an endarteritis which leads to obliteration of the capillaries. The process differs from an ordinary arteriosclerosis in the disappearance of muscle-cells with thickening of the middle layer by the growth of fibrous tissue. The endothelium proliferates and contracts the lumen. The walls thicken by the deposition of the granular material, which later becomes homogeneous. Finally complete occlusion results, and the capillaries involved are converted into glistening, compact, homogeneous tissue. He designates the process as "*vasculitis capillaris obliterans*." The deposit in the blood-vessels is a hyaline substance similar to that found in other forms of arteriosclerosis.

The sequelæ to the alterations in the kidney are identical with those which follow contracted kidney due to other causes, and which are described in the section on the kidneys.

Lead arthralgia is not accompanied by any constant or characteristic lesion. In lead gout, uric acid may be deposited in the contracted kidneys and in various joints.

Lead paralysis, although common in chronic poisoning, is not constant. The musculospiral nerve is the first and often the only one involved. So constant is this that paralysis of this nerve or its branches is generally regarded as due to lead, even when inquiry fails to reveal the manner in which the poison has been introduced.

"Drop-wrist" may result from the external application of preparations containing lead, as happens in the use of certain cosmetics, as well as when the poison is taken by the mouth. Atrophy of the muscles usually follows paralysis, but in some instances the atrophy may precede paralysis. Very rarely the deltoid or the biceps is more seriously affected than the muscles of the hand and wrist. The peroneal muscles are sometimes affected in lead paralysis. General paralysis as a result of lead poisoning has been reported. Paralysis of one or both vocal cords is said to be a typical symptom of lead poisoning in horses, and paralysis of the adductors of the larynx has been observed in men. Atypical paralyses are likely to result from the combined action of two or more poisons, as lead and alcohol or lead and syphilis.

Examination of the parts involved in lead paralysis shows changes in the muscles, blood-vessels, and nerves. The alterations in the muscles may be macroscopic. They are much wasted and pale or yellowish. Microscopically certain fibers will be markedly altered, while others are quite normal. The diseased fibers are shrunken and sometimes show an enormous proliferation of nuclei. The position of a fiber may be indicated only by the presence of granular debris and clusters of nuclei. The changes in the vessels are those of arteritis obliterans. Changes in the nerves are most evident in their peripheral terminations, but may extend backward to the trunks, and are those seen in other forms of neuritis.

Lead encephalopathy is a term used to designate a form of chronic lead poisoning accompanied by symptoms referable to disturbances of the brain, as delirium, melancholia, convulsions, and coma. It is a question whether this condition is due to the direct action of the lead on the brain-cortex or results from the general arteriosclerosis and changes in the kidney. Be this as it may, the most exhaustive researches have failed to show either gross or minute lesions in the brain.

Mercury.—Mercurial compounds are generally divided into mercurous and mercuric preparations; the latter are the more poisonous. However, the difference in action is one of degree rather than of kind. While very large doses of calomel may be given without harm, its continued employment is not free from danger, and even metallic mercury in a finely divided state has been known to cause death in at least two instances. The ethyl compounds of mercury are exceedingly poisonous, and two chemists have lost their lives in experimenting with them. Mercuric chlorid owes its corrosive action to the avidity with which it combines with proteids, and all mercury preparations enter the blood in the form of an albuminate. This is also true of the metal itself. When absorbed from a mucous membrane or through the unbroken skin, albuminous compounds are formed. It must not be supposed, however, that the poisonous action of mercury is dependent upon the formation of proteid compounds, or that saturation with albumin renders mercury inert. The albuminate itself is poisonous and may induce stomatitis, salivation, and enteritis.

In acute mercurial poisoning, whatever may have been the method of administration, there will be a brownish or black coloration of the gums and marked inflammation with ecchymoses in the mucous membrane of the alimentary canal. Death may occur within a few minutes from the administration of a very large dose. In such a case the histologic changes are not likely to be prominent; but in the majority of instances death is delayed for two or three days, possibly longer. When a large dose of corrosive sublimate is taken, the effect may resemble that induced by mineral acids. There may be most violent inflammation of the mucous membrane of the mouth, pharynx, and larynx, with consequent edema of the glottis. The

erosions in the stomach and intestines may be extensive and deep, even to perforation. Ulceration of the ileum and a diphtheritic condition of the large intestine, with and without perforation, have been observed. Frequently the mucous membrane, from the mouth to the pylorus, is found diffusely colored. Ludwig reports a case in which the mucous membrane of the esophagus and stomach looked as if it had been cooked. The bronchial tubes are often highly inflamed, and ecchymoses on the endocardium are found; while degeneration of the muscle of the heart has been seen, even when death resulted within two or three days. The marrow of the bones may be highly injected. Ulcers soon form on the gums, and the kidneys and liver show lesions which will be described later. According to Virchow, the anatomic changes in the large intestine cannot be distinguished histologically from those of acute dysentery. Chemically mercury can be detected in the tissues. However, the intestine is not invariably seriously involved, as cases have been reported by competent observers in which no changes or only those of very slight degree could be detected. Indeed, there are rare instances in which very large quantities of corrosive sublimate have passed through the alimentary canal without more harmful effect than a severe purging. The writer knows of a fortunate case of this kind, where a man swallowed a tablet containing seven and one-half grains of corrosive sublimate, mistaking it for quinin. According to Kaufmann, involvement of the intestinal walls depends upon the formation of thrombi in the capillaries, with consequent necrosis, while the diphtheritic condition is ascribed to the action of bacteria. In acute poisoning from administration by the mouth, peritonitis with bloody serous exudate may occur.

The changes in the kidney are most interesting. If a section of this organ be placed under the microscope and treated with dilute sulphuric acid, effervescence takes place and the formation of crystals of gypsum may be seen. This is due to the fact that in mercurial poisoning calcification occurs in the renal epithelium.

In very acute cases the kidneys are hyperemic and frequently show hemorrhagic spots. When the poisoning is less rapid, the condition resembles that of an acute parenchymatous nephritis. On microscopic examination there will be found cloudy swelling and necrosis of the cortical tubules. Fatty changes may or may not exist. Hyaline or granular casts may be found in the tubules, and the interstitial connective tissue may be infiltrated with small cells. Deposits of lime are found in the tubules, most abundantly in the convoluted ones. The question has arisen whether or not this calcification of the kidney can be regarded as pathognomonic of mercurial poisoning. Weichselbaum states that it cannot be so considered, because it is seen in poisoning with other substances, as manganese, bismuth subnitrate, glycerin, etc.; but he adds that the finding of abundant chalky deposits in the convoluted or straight tubules of the cortex should be considered a strong suggestion of mercurial poisoning. The cause of these deposits is another interesting question. The old theory that the lime deposited in the tubules is withdrawn from the bones has been shown to be erroneous. Kaufmann offers his theory of thrombosis in explanation, but it is more rational to explain the calcification by the supposition that the epithelium injured by the mercury is no longer able to eliminate the lime salts of the urine. This, with the diminished secretion of urine, which may lead to anuria, is probably sufficient cause for the formation of the deposits. In

this connection it is interesting to state that the researches of E. Ludwig have shown that the places of predilection for the deposition of mercury are the kidneys, liver, and walls of the large intestines, in the order named.

Muscular tremor is one of the common manifestations of chronic mercurial poisoning. Paralysis of the upper extremities may occur; it is not accompanied by atrophy, and microscopic examination of the nerves shows cloudiness and granulation of the neurilemma without alteration of the axis-cylinder.

The malar necrosis resembles that due to phosphorus. There is much difference of opinion concerning the effect of chronic mercurialism on the bones; since so many of the individuals in whom these lesions have been studied were syphilitic, it is difficult to decide to what extent the bone-lesions should be attributed to this disease or to the effect of the mercury.

Copper.—Metallic copper is not poisonous unless it be taken in finely divided form, when the gastric juice may dissolve it in sufficient quantity to prove injurious. All the salts of copper, however, are poisonous.

In acute poisoning with copper, the mucous membrane of the whole alimentary canal is inflamed and changed in a greater or less degree. Ecchymoses may be found anywhere along the tract. Ulceration may occur in the stomach, small or large intestine, and may proceed to perforation. Patches of green or bluish coloration may be seen here and there. The hemoglobin of the blood is more or less broken down, with the formation of an excess of bile-pigment leading to marked icterus. Unless death occur within twenty-four hours, there may be found fatty changes in the liver and kidney, the latter organ showing also the appearances of acute parenchymatous degeneration. The poison, albumin, casts, blood-pigments, and bile-pigments may be found in the urine.

Zinc.—The chlorid is the only actively corrosive compound, but all the salts are poisonous. The mucous membrane of the alimentary canal, especially that of the stomach, is inflamed and corroded. The corrosive action of zinc chlorid is characterized by the formation of a hard, dry crust which remains in place. The walls of the stomach are hardened and contracted. The kidneys show a parenchymatous degeneration. Albumin and casts are found in the urine. Chronic zinc poisoning among those engaged in smelting has been frequently reported, but it is questionable how much of the ill effect is due to zinc and how much to associated metals, as lead and arsenic.

Aluminum.—Practically alum is the only salt of aluminum from which poisonous effects are likely to result. This is true merely because alum is the only soluble salt of aluminum that is widely used. All salts of aluminum are poisonous when injected subcutaneously or intravenously. The researches of Siem, confirmed by those of Döllken, have demonstrated that the lesions induced by the subcutaneous administration of salts of aluminum are extensive and serious. In animals they found the lesions of "metallic kidney" and fatty changes in the anterior horns of the spinal cord.

Silver Nitrate.—The only preparation of silver from which poisoning has resulted is the nitrate. In acute poisoning with this salt, its caustic action is responsible for the most prominent lesions. The nitrate of silver in strong solution or in the form of lunar caustic produces a more or less deep eschar when brought in contact with tissue. On portions of the body exposed to the light, this eschar soon turns brown or black, while on the mucous membrane it remains white. The eschar consists of the albuminate of silver,

and the change in color on exposure to light is due to reduction of the salt to metallic silver or one of the lower oxids. Postmortem examination after acute poisoning shows only escharotic lesions in the mucous membrane.

Chronic poisoning with silver is known as argyria and is of great interest to pathologists. Since the publication in 1859 of the now classic paper of Frommann, on the pathologic lesions of argyria, much interest has been manifested in this subject. Nitrate of silver was formerly of some repute in the treatment of epilepsy, and many cases of argyria resulted from its employment in this disease. Argyria may result from the long-continued employment of nitrate of silver in any disease. In a case of ulcerative colitis treated at the hospital of the University of Michigan, the colon was washed daily with a solution of silver nitrate (1 dram to 4 pints), and well-marked argyria appeared within eight months. The subject of Frommann's studies had taken about three and one-half ounces of this salt in pill form within about ten months. During the greater part of this time, he took one six-grain pill each day. The face began to show evidences of pigmentation about two months after the treatment was begun. The coloration gradually deepened and extended to other parts of the body. A chronic gastritis developed, accompanied by pain, which at first was intensified only on taking one of the pills, and later by food. There was frequent vomiting, and restriction to liquid food was found to be necessary. It is interesting to note that the patient developed tuberculosis while thus saturated with silver.

The only parts of the skin free from pigmentation were the palms of the hands and the soles of the feet. In the brain the Pacchionian bodies were prominent, the arachnoid showed some cloudiness, and the choroid plexus was grayish blue. Pigment indurations and calcified tubercles were found in the lungs, along with cavities and miliary tubercles. The walls of the left ventricle of the heart were much thickened. The mucous membrane of the stomach was reddened and dotted with small hemorrhagic erosions, while one oval ulcer 7 cm. long and 5 cm. broad occupied the posterior wall midway between the cardia and the pylorus. The floor of this ulcer was uneven, and at one spot it consisted of the pancreas, the stomach being perforated and adherent to this organ. There was a stricture of the pylorus, apparently due to hypertrophy of the muscular and submucous layers.

The mucous membrane of the small intestine was thin, and the intestine itself was contracted. The follicles were filled with black granular deposits. Under the microscope these granules were found to vary much in size and form, but none was crystalline. On treating a thin section containing these granules with a solution of potassium cyanid, they disappeared. Similar granular deposits were found to be abundant in the spleen.

The liver was small, full of blood, and contained cells undergoing fatty changes. Granular deposits were observed in the middle of the acini, apparently surrounding the small veins. On microscopic examination of a cross-section of the small vessels, the lumen was seen to be enclosed by a black ring. The coloration was in part granular and in part diffuse.

The deposits of silver seemed to be most abundant in the kidneys, and it is to these organs that students of argyria have subsequently given most attention. Frommann found that the pyramids were stained dark gray, the color being deepest near the papillæ and becoming lighter toward the cortex. On section of the cortex the glomeruli appeared as black dots. Micro-

scopically they were seen to contain finely granular material which conformed to the shape of the vessels and was quite distinct from the capsule. Some glomeruli were more intensely colored than others. Unchanged Malpighian bodies were found to be few. The same finely granular material observed in the blood-vessels was found deposited on and between the walls of the tubules of the pyramids. Toward the papillæ these deposits were most abundant, becoming less toward the cortex, but not disappearing altogether. On cross-section the tubules appeared, each surrounded by a broad black ring. The walls of the convoluted tubules showed no abnormality except fatty epithelium. These granular deposits dissolved in solutions of potassium cyanid, and became white and opaque on the addition of nitric acid, and again black on subsequent treatment with ammonium sulphid. Other investigators have confirmed the statements of Frommann, but von Kahliden finds the histologic changes in the kidneys to be more marked than others have supposed. It might be conjectured that the individual from whom von Kahliden obtained his material suffered from some co-existent disease to which these lesions might be attributed; but he points out that the distribution of the histologic changes corresponds exactly with the deposits of silver, and moreover he has found a similar condition in a rabbit in which argyria had been induced experimentally. It is highly probable that Frommann and others have been so much interested in the study of the deposits that they have given insufficient attention to the observation of co-existent degenerative changes. The changes observed by von Kahliden may be stated as follows: In the places containing the granular deposits, and only in these, the connective tissue is markedly increased—from six to eight times the normal. Within the hyperplastic regions the straight tubes are much compressed and their epithelium exfoliated. At the same time the hyperplastic tissue undergoes hyaline degeneration, and this is followed by calcification, which involves not only the altered connective tissue, but also the epithelium of the tubules as well.

Rierner supposes that the silver compound is reduced in the intestine, and the finely divided metal is taken up by the blood and lymph and mechanically deposited; but Naunyn has shown that the distribution is wholly different from that which occurs with a finely divided pigment. Loew thinks that silver is reduced in the body only by the living cell, that Rierner is in error when he states that the silver is never found combined with cellular elements or deposited in them, and that a more exact study of the blackened glomeruli shows that the silver is deposited in the endothelial cells surrounding the Malpighian bodies. He also states that the text-book assertion that the epithelium of the glomeruli is impermeable to finely divided particles, founded upon Rierner's studies of argyria, is erroneous.

In the kidney the deposit of silver is always most marked around the afferent vessels of the glomeruli.

Rozashegi has studied the lesions induced in animals by chronic poisoning with salts of silver. He found the mucous membrane of the trachea and larynx usually hyperemic, sometimes purple red. In the lungs, hyperemia and edema were marked. In many instances there were hepatized areas, and in one a caseous focus. The pulmonary epithelium showed fatty changes, while the connective tissue of the walls of the alveoli showed proliferation. The liver exhibited principally cloudy and fatty changes and consecutive hyperplasia of the interlobular connective tissue. The epithelium

of both the convoluted and the straight tubules of the kidneys was swollen and granular, and the detritus resulting from disintegration filled the lumen. Fatty changes of the epithelium were seldom observed, and then existed only to a slight degree in the convoluted tubules. The striated muscles were soft and pale; the striations were frequently found displaced. The muscle-sheath sometimes contained large drops of fat.

Chromium.—Those compounds in which chromium acts as a base are only feebly poisonous, while those in which it plays the part of an acid are markedly active. Chrome-alum and chromium hydrate, known as Guignet's green, are the best known compounds of the first group. The alum is harmful only in large quantities; and the green, when free from mixture with boric or picric acid, is wholly insoluble and inert. On the other hand, chromic acid and the chromates are actively poisonous, as a dose of one-half grain of the bichromate of potassium may cause unpleasant effects. Chromic acid is a powerful caustic, and all the chromates induce more or less local reaction.

In acute poisoning the vomited matter is green or blue, on account of the reduction of the chromium by organic matter. Either of these colors in vomited material may possibly be due to altered bile-pigment; but when blood and shreds of mucous membrane from the stomach are present in green or blue vomit, the possibility of chromium poisoning should not be forgotten. The stools are watery and stained with blood-pigment. The urine is diminished in amount and contains albumin and casts. The skin may become icteric in a few hours after the administration of a poisonous dose.

The mucous membrane of the mouth in acute poisoning is swollen and sometimes quite detached from the subjacent tissue. The gums are often stained bluish green. The lining of the esophagus may be highly inflamed, while that of the stomach is swollen, detached in places, and ecchymosed; erosion may extend to the deeper tissues. Hyperemia and ecchymosis of both the small and large intestines are generally found. The peritoneum may be inflamed and the cavity may contain a blood-stained serous exudate. The mucous membrane of the bladder may show hemorrhagic spots, and, when death is delayed for a few days, ulceration. The bronchial tubes may be involved in the general inflammatory condition, and effusion into the ventricles of the brain may occur. The blood becomes brownish from the action of the poison on the hemoglobin, and methemoglobin is formed along with the other decomposition-products. The liver-cells speedily undergo fatty changes, but the alterations in this organ in acute chromium poisoning have not been closely investigated. This form of intoxication has been employed by Gergens and by Posner in the study of acute inflammatory processes accompanied by the formation of casts in the kidneys. Animals are treated subcutaneously with from 0.25 to 0.4 gm. of the neutral chromate of potassium dissolved in from 2 to 4 gm. of distilled water. A few hours after the injection the kidneys show no macroscopic changes of importance, but the microscope reveals an interesting condition. The epithelium of the convoluted tubes shows cloudy swelling and ragged borders. The glomeruli are moderately injected and their capsules contain a larger or smaller volume of an exudate which is coagulable on the application of heat. Various elements are detected in the contents of the tubules, especially a large number of round cells enclosed in a fine network, apparently due to the coagulation of some albuminous fluid. This is believed to illustrate the formation of casts in these tubules. Posner concludes from

his studies that fibrinous masses may be formed in the tubules at a time when the epithelial cells, although not in a normal condition, are certainly not absolutely necrotic.

Instances of chronic poisoning have been observed after the employment of a chromate in the treatment of disease, as in the Guntz cure for syphilis; J. Wm. White has recorded a fatal result from the application of chromic acid to a large number of condylomas about the buttocks and vulva. But poisoning is most common among workmen engaged in the industrial use of chromium compounds. Injurious effects may follow the external application and the inhalation of these preparations, as well as from ingestion through the alimentary canal. When taken by the mouth, contracted kidney with its sequelæ is one of the most prominent and disastrous effects. Externally it leads to ulceration of the hands, arms, inside of the thighs, etc. Furuncle, eczema, impetigo, and pseudopsoriasis are given by Kobert as frequently observed accompaniments of ulceration of the skin. The drum of the ear, more frequently the septum of the nose, may be perforated. An ulcerative conjunctivitis has been observed, and the inhalation of the poison in the form of dust leads to bronchitis. Deep ulcers often form in the pharynx.

Nickel and Cobalt.—Soluble salts of nickel and cobalt are poisonous. The most constant lesions are blood-extravasations in the stomach, intestines, and in the epicardium and endocardium. In acute cases there are no changes in the blood, while in chronic poisoning both the corpuscles and the percentage of hemoglobin are diminished. Small coagula are frequently observed in the heart.

Barium Chlorid.—Practically the only salt of barium ever used for its poisonous effect is the chlorid. In the intensity of its action this substance equals white arsenic. Kobert finds records of twenty-six cases of poisoning with barium salts, and of these about half terminated fatally. Some years ago the writer saw a woman who had taken with suicidal intent about twenty grains of barium chlorid. The early recognition of the nature of the poison, some of which was found in the room, prevented serious results.

Barium chlorid acts as an irritant, but is most harmful in its effects upon the nerve-centers. The nausea and diarrhea which appear are in part the result of its action on the ganglia of the intestine. It has a digitalis-like effect on the heart. The heart beats very slowly and so violently that its movements may be seen and even heard at some distance. As a consequence of this enormous increase in blood-pressure, ruptures and hemorrhages in diverse organs may occur.

At autopsy no changes are observable, at least not constantly, in the mouth or esophagus; but the stomach is reddened and ecchymoses may be extensive in the intestines. As has already been indicated, small hemorrhages may be found in the lungs, in the walls of the heart, in the cord and brain, and in their meninges. When administered hypodermically or intravenously, barium chlorid is eliminated by the stomach and intestines and causes local irritation in these organs. In animals experimentally poisoned with this substance, thrombi caused by the insoluble sulphate have been observed, and granular deposits of the same salt have been found in the kidneys. These findings have not, however, been reported in man.

Potassium Chlorate.—The reckless manner in which this salt was used a few years ago, and is still employed by some, caused much harm. Potassium chlorate should never be administered internally, and as a gargle

in various affections of the throat there is no justification for its employment, and it should be supplanted by more scientific and less dangerous treatment.

Potassium chlorate owes its poisonous properties to the fact that it converts the hemoglobin of the red blood-corpuscle into methemoglobin. The readiness with which this action goes on depends on several conditions. The higher the temperature, the more rapidly does the poisonous action manifest itself; therefore it is especially harmful when administered in fevers, exactly the condition in which it has been most extensively prescribed. Again, decreased alkalinity of the blood favors the poisonous action of potassium chlorate. The dyspnea which often accompanies the throat-affections in which this salt has been so widely used decreases the alkalinity of the blood by interfering with the elimination of carbonic acid gas. The simultaneous administration of dilute preparations of the mineral acids has a similar action. Thirdly, the density of the blood influences the action. By the addition of such indifferent substances as sodium chlorid, glucose, and serum albumin, the intensity of the effect is magnified.

With relatively small doses the transformation of hemoglobin begins within the corpuscle; but with larger quantities the equilibrium between the formed elements and the plasma is destroyed, and the corpuscles go to pieces and the transformation continues in solution. The débris of the disintegrated corpuscles accumulates in various organs, interrupting their functions; and at the same time, the oxygen-carrying power of the blood being diminished, disturbances of metabolism necessarily result.

In the most acute cases, which have generally resulted from mistaking the chlorate for purgative salts and swallowing large quantities in a fasting condition, death results within a few hours. Vomiting, diarrhea, dyspnea, marked cyanosis, and weakness of the heart's action are the most prominent symptoms.

In acute cases the only constant change found after death is that resulting from the action of the poison on the red corpuscles; the blood is thick and brown.

In less acute cases, such as have been observed from its excessive use in throat-affections, the detritus resulting from the disintegration of the red corpuscles will be found collected in such organs as the kidney, spleen, liver, and bone-marrow, which are generally swollen. The skin is icteric, and grayish-violet spots may be seen. Often the corpuscles which are not broken appear as though they contained nuclei; some are quite pale. The bone-marrow is brown and filled with disintegrated corpuscles. Both the straight and convoluted tubules of the kidney are filled with cylinders made up of cellular detritus.

The chlorates of sodium, magnesium, and calcium are poisonous, but are less so than the potassium salt.

The Mineral Acids.—The local effects of the mineral acids are dependent upon the concentration rather than upon the amount. When applied to the skin or brought in contact with mucous membrane, the concentrated mineral acids destroy the tissues. When thus applied during life, the area of contact is soon surrounded by one of inflammation. When applied after death, the tissue is also destroyed, but there is no evidence of consequent inflammation. When a concentrated mineral acid is swallowed, the mouth and stomach generally show the most marked effects. The esophagus may escape with only slight irritation. When the quantity swallowed is not large, the acid passes down the esophagus and along the smaller curvature of

the stomach toward the pylorus. The most noticeable changes will be found along this line, and the frequency of pyloric ulceration and stenosis after poisoning with the strong mineral acids is thus explained. When the lesions in the stomach are not sufficient to cause speedy death, the gastric juice may digest the portions of the walls over which the mucous membrane has been destroyed, and thus lead to perforation.

The poisonous effects of the mineral acids are not wholly confined to the local destruction of tissue; they may cause death by diminishing the alkalinity of the blood. The life of herbivorous animals is speedily jeopardized by increasing the amount of acid in the body; while the carnivorous animals and man will bear large quantities of acid, provided it be administered sufficiently diluted. This difference is explained by the fact that carnivorous animals may, in case of need, supply a large amount of ammonia, which will neutralize the acid. Indeed, the greater part or all of the nitrogen generally eliminated by man in the form of urea may appear in the urine in the form of ammonia combined with some acid. The need of the body's ability to furnish ammonia to neutralize acid is seen in some forms of diabetes, in which the quantity of oxybutyric acid formed within the organism is large.

Sulphuric Acid.—The ease with which this acid can be obtained under the name of the oil of vitriol, and the popular knowledge of its action, have made it an agent frequently employed in suicide, especially in former times. Moreover, it is altogether probable that the extensive destructive action of the acid has had a fascination for the diseased mind intent on suicide. Quite naturally its employment in homicide has been very rare. The acid is sometimes thrown into the face, and it has been injected into the vagina and rectum.

When concentrated sulphuric acid is brought in contact with the skin, there is severe pain and the spot turns first white and then brown; after a few minutes the adjacent skin becomes red and swollen. The epidermis is soon destroyed, and the destructive action may extend to the deeper tissues. In the case of a man who attempted to swallow a large quantity of the acid, spasm of the pharynx prevented his doing so, and the fluid ran from the mouth over the chin and neck. The destructive action on the tissue was so great that the resulting scar bound the chin down upon the breast, and a plastic operation was necessary. When the area of skin destroyed by contact with the acid is great, intestinal ulceration develops, as it does after extensive burns, and the individual falls into a somnolent condition, leading to coma and death. This is undoubtedly due, as it is in extensive burns, to alterations in the blood.

When the acid is thrown into the eyes, conjunctivitis and keratitis result, followed by glaucoma, often leading to blindness.

In case of death from swallowing the acid, brownish marks are frequently seen extending from the corners of the mouth, over the lower jaw, and down upon the neck. The lips are excoriated or uniformly parched brown. The mucous membrane of the mouth and tongue is covered with a white or brown layer of altered tissue. The acid actually burns the tissues and destroys their histologic elements. In the stomach similar changes are found, but the destructive action is deeper than in the mouth. Frequently the wall is pierced through and the effects of the acid may be seen on adjacent organs; perforation has been reported in about one-third of the cases. Black spots consisting of decomposed blood-pigment may be

seen in the stomach, and, in case of perforation, in the peritoneal cavity. The alterations in the intestines resemble those found in the stomach, but are less intense and gradually grow less marked in the lower portions. Parenchymatous inflammation develops in the liver and kidneys.

Chronic poisoning with dilute sulphuric acid is rare, but according to Kobert it occurs in France from two causes. He states that in the lowest drinking-places this acid is added to brandy to make it "bite," and that it is also added to wine to "improve" it. According to Weiske, chronic poisoning in animals is accompanied by the withdrawal of lime salts from all the bones except the vertebræ and the skull.

Kobert states that chronic poisoning with the acid sulphates of lime and potassium, which are formed in wine on the addition of dilute sulphuric acid for the purpose of precipitating the gypsum, may occur. He also thinks that the acid sulphate of lime is an important factor in death from inanition in herbivorous animals. The sulphuric acid which results from the oxidation of the sulphur of the proteid tissue is insufficiently neutralized. According to the same authority, the substance sold as the neutral sulphate of potassium is frequently employed in England and France, and sometimes causes death. Section shows the stomach and intestines inflamed. This effect is attributed to the presence of the acid sulphate or to impurities, as zinc and copper.

Nitric Acid.—This acid is largely used in various manufactures, and medical literature contains the records of about 400 cases of poisoning, mostly accidental. Nitric acid colors the skin yellow, and this becomes orange on the addition of ammonia. The coloration of proteid material by nitric acid is known as the xanthoproteic reaction.

When the acid is taken in solution of 20 per cent., or more dilute, the local effects are not prominent. When the concentration reaches 33 per cent., or is greater, the local effects are similar to those of sulphuric acid, excepting the yellow coloration. In the intestines the mucous membrane is stained gray or grayish white, and this is regarded by Lesser as important in distinguishing between poisoning with this acid and with chromates. The stomach may be perforated and the abdomen distended with gas. The kidneys show an acute parenchymatous nephritis.

According to Bellin, nitric acid in daily doses of from 10 drops to 15 gm. is used in Russia as an abortifacient. Chronic poisoning results from the treatment, and is characterized by tremor, insomnia, marked anemia, gastric catarrh, and diminished secretion of urine. In two cases section has shown fatty changes of the heart, nutmeg liver, enlargement of the spleen, nephritis, and effusion beneath the meninges of the brain. It is possible that some of these effects may have been due to arsenic in the acid.

Hydrochloric Acid.—Lewin finds reports of twenty-six cases of poisoning by this acid; one was a homicide. Stricture of the esophagus is frequent, but perforation of the stomach is rare, although it may occur. Kobert states that purulent mediastinitis and exudative pleuritis result. Fatty changes of the liver and nephritis have been observed. A chronic auto-intoxication from hypersecretion of this acid in the stomach is regarded as possible, but on this point we have no positive knowledge.

Lehmann found that an atmosphere containing one part or more per thousand of the vapor of hydrochloric acid causes in animals a flow of tears, conjunctivitis, and cloudy swelling of the cornea. The duration of exposure necessary to induce these effects varies with the ability of the animal to

protect the eye completely by closure of the lids. The tears were observed to be milky, and microscopic examination revealed the presence of fat globules, believed to come from the Meibomian glands. The mucous membrane of the nose is inflamed, and some days after the exposure a purulent nasal catarrh may set in and lead to a dry necrosis or a moist gangrene involving the septum and the alæ and causing rather extensive destruction. This effect is supposed to be due to the local action of the gas upon the blood-supply of these parts. In some animals the salivary glands are greatly stimulated. In animals dying during the experiment or killed soon after exposure, the trachea was pale with a few ecchymoses. The bronchial tubes contained a thin, frothy secretion. There was uniformly an emphysematous condition, and pneumonic changes were observable in animals that survived the exposure twenty-four hours and longer. In all the guinea-pigs exposed to an atmosphere containing one part per thousand or more of the gas, hemorrhagic spots were found in the mucous membrane of the stomach. Slight ecchymoses were observable in Peyer's patches in two animals—a rabbit and a guinea-pig.

Chlorin and Bromin.—Researches of Lehmann on poisonous gases convinced him that chlorin and bromin are both qualitatively and quantitatively alike in their effects upon the animal organism, while they differ widely from the vapor of hydrochloric acid. The effects upon the eyes and upon the mucous membrane of the nose and mouth are much less marked than those of the acid, and necrosis of the septum and alæ of the nose did not occur in any instance. The effects of these gases are most evident in the lungs. Even when the atmosphere contained only 0.01 : 1000 of either of these gases, and after an exposure of six and one-half hours, there developed after twenty-four hours a mucopurulent bronchitis with pneumonic foci and marginal emphysema. Edema of the lungs was much more constant and pronounced than in poisoning with either ammonia or hydrochloric acid vapor. Especially marked was the macroscopic filling of the perivascular lymph-spaces about the larger pulmonary vessels. When the percentage of the gas was increased, a typical croupous membrane formed, and in some instances was continuous from the larynx to the finest bronchi. When the amount of gas reached 0.3 : 1000 and the exposure continued for one hour or longer, the membrane was invariably found. Great dyspnea and stupor were marked symptoms.

Hydrogen Sulphid.—The frequency with which man is exposed to the action of this gas, one of the products of many putrefactive bacteria, renders a study of its poisonous effects of great interest. Hydrogen sulphid, when given off from decomposing matter, is generally mixed with other gaseous products of putrefaction, as CO_2 , CO , and NH_3 ; and the effects may be exceedingly variable, according to the relative amount of each of these present. Moreover, an atmosphere largely contaminated with these gases is generally poor in oxygen, and this deficiency has its own ill effects. Accidental poisoning with the pure gas occasionally occurs in laboratories.

The injurious effects of hydrogen sulphid are probably underestimated by those who have neither tested its action nor acquainted themselves with the literature of the subject. The writer has repeatedly observed its effects in sterilized bacterial cultures when its presence was hardly perceptible to the sense of smell and when silver or lead paper placed over the test-tube blackened very slowly. Boutny and Descout found that 1 c.m. of very

filthy water yielded 140 c.c. of H_2S on being agitated, and 46 c.c. more on being boiled. From this they conclude that 1 c.m. of the water would furnish enough of this gas to render 28 c.m. of air fatally poisonous. That both men and animals may acquire marked immunity to this poison is undoubtedly true. Dupuytren and Thénard found an air containing 0.66 : 1000 of this gas poisonous for birds, 1.25 : 1000 poisonous for dogs, and 4 : 1000 poisonous for horses. Biefel and Polek found that a rabbit died after 75 minutes' exposure to an atmosphere containing 0.59 : 1000 of H_2S , and another rabbit died after an exposure of two hours to air containing only 0.37 : 1000.

Lehmann has made some valuable experiments upon the poisonous effects of this gas. He employed a Pettenkofer-Voit respiration apparatus. All the animals showed signs of local irritation after prolonged exposure to air containing only 0.13 : 1000. A narcotic effect was evidenced by the position taken by the animals. Paralysis gradually developed and death resulted from failure of the respiration. In cats, death was preceded by a restless sopor. Under doses of 0.72 : 1000 there was great dyspnea accompanied by convulsions, sometimes with opisthotonos. In all of these cases death was not due to paralysis of the nerve-centers solely, but in part to simultaneous changes in the lungs. At first the respiration became slow, then with increasing dyspnea it became very rapid. Section showed edema of the lungs in all animals exposed for some hours to the action of the gas. The lungs were voluminous, diffusely dark red, and showed punctiform blood-extravasations. The fluid of the edematous lungs was very abundant, stained with blood, and often ran from the mouth before death. Marginal emphysema was seldom absent, and in some instances was highly marked. Together with the edema, there was frequently a pleuritic effusion.

Edema of the lungs is not seen in the apoplectic poisoning with hydrogen sulphid which occurs when animals are exposed to an atmosphere containing a large amount of the gas.

Death from sewer-gas containing a large amount of hydrogen sulphid is often instantaneous and leaves no constant changes except that the blood is fluid and dark. Generally all the chambers of the heart contain fluid blood.

Hydrocyanic Acid.—Compounds yielding hydrocyanic acid under certain conditions are widely distributed in the vegetable world. Poisoning, however, is very rarely due to these substances. The official dilute hydrocyanic acid, containing 2 per cent. of the acid, is quite properly but little employed. Most cases of poisoning are accidental and come from the cyanids so largely used in the arts, rarely from the dilute acid.

Hydrocyanic acid, either free or combined with potassium, is one of the speedily fatal poisons. The writer has seen animals die within thirty seconds from the effects of large doses. It rapidly diffuses throughout the body and appears in the excretions. Its odor is easily detectable in the exhaled air. In making postmortem examination when this poison is suspected, the odor given off from the stomach and other cavities of the body is of great significance, and the pathologist should bear in mind that the inhalation of the gas from the dead body is not altogether free from danger. At least one case is recorded in which serious poisoning occurred in this way. There is no proof that hydrocyanic acid is decomposed in the body, and in nonfatal cases the whole of the poison is believed to be eliminated unchanged.

In poisoning in man, it is customary to speak of three stages. The first is characterized by dizziness, headache, and precordial pain; the second stage, known as the asthmatic, is marked by great difficulty of respiration; and the third, known as the convulsive, appears when the now unconscious victim is seized with violent convulsions. However, when a large amount is given, there are only a few spasmodic attempts at respiration, and life is extinct.

The dead body usually shows areas of bright-red coloration. According to Kobert, these spots are due to the presence of cyanomethemoglobin, a compound having a characteristic spectrum resembling that of reduced hemoglobin, but not identical therewith. On cutting into the tissues, however, the blood of the subcutaneous structures and of the viscera is found to be dark red, unless the quantity of the poison taken has been very large; in which case the blood throughout the body may be bright red. Whether the blood be light or dark, most of it will be fluid, and it has only slight tendency to coagulate.

The mucous membrane of the stomach is generally injected: sometimes uniformly, and in other instances only over limited areas. The right side of the heart is generally filled with blood, while the left is empty. The lungs are sometimes edematous, and there may be effusions into the ventricles of the brain. The urine is likely to contain blood and sugar, along with an unknown reducing substance. The characteristic odor can often be recognized in the urine.

Cyanogen gas and the iodid of cyanogen are poisonous, inducing effects similar to those resulting from hydrocyanic acid. Sulphocyanid of potassium is generally regarded as inert; but in very large doses it resembles hydrocyanic acid in its action on the blood. This is of special interest on account of the fact that it is a normal constituent of the saliva and of the urine.

Carbon Monoxid.—This substance, which is the most poisonous constituent of so-called coal-gas, has caused many deaths; and without doubt it is responsible for many fatalities attributed to other causes. It has been largely employed for suicidal purposes, and many instances of accidental poisoning with it are known. In the five years from 1848 to 1852, in France 1401 persons intentionally killed themselves by inhaling this gas. Illuminating gas made from coal contains from 5 to 10 per cent. of CO, while that made from wood may contain as much as 60 per cent. Water-gas, now so largely used for illuminating purposes, contains about 30 per cent. Organic dust, falling upon heated stoves, burns with the evolution of appreciable quantities of CO. There has been some difference in the statements concerning the amount of this gas necessary to render harmful the inhalation of air containing it. The most exact experiments place it at about 0.02 per cent.

The most poisonous effect of CO results from the readiness with which it combines with hemoglobin and from the stability of the compound thus formed. The affinity of CO for hemoglobin is about two hundred times greater than that of oxygen. From this it will be seen that, even when the inhaled air contains only traces of CO, this substance is retained and accumulates in the blood. It should be distinctly understood that, even in fatal poisoning with this gas, the greater part of the hemoglobin remains in combination with oxygen. The writer recently saw a report of a case of poisoning with CO, in which the statement was made that there was no oxyhemoglobin in the blood; and yet this was not a fatal case, and the patient lived

for months and continues to live, so says the paper, without oxyhemoglobin. Such a statement as this is absurd. Death results when the respiratory capacity of the blood is reduced from 20 to 30 per cent. Saturation of the hemoglobin of the blood with CO during life is impossible.

In recovery from slight poisoning with this gas, it is slowly dissociated from the hemoglobin and exhaled. It is not oxidized to carbonic oxid gas. The corpuscles the hemoglobin of which is combined with CO retain their normal form and are not immediately disintegrated, but are destroyed more quickly in the liver than are the corpuscles the hemoglobin of which is in a normal condition. The lethal quantity of CO for a man weighing 70 kilograms is computed by Dresser at 0.8 gm., from his experiments on rabbits. The whole of the gas inhaled is not held by the hemoglobin; some of it is dissolved in the plasma, and some of it penetrates the tissues, and may, according to Fehling, pass from the mother to the fetus.

CO hemoglobin gives off no oxygen to the tissues, and the symptoms induced are partly those of asphyxiation. Blood containing this gas is of a cherry-red color, and this may be observed in some instances many days after death. The spectrum of CO hemoglobin shows two dark bands between the lines D and E, and is similar to the spectra of oxyhemoglobin and hemochromogen. However, these spectra are not identical, and with all of them in view they can be easily distinguished. The oxyhemoglobin spectrum lies farthest to the left, that of hemochromogen farthest to the right, extending slightly beyond E, while that of CO hemoglobin lies between. Furthermore, the lines are not so widely separated as in the oxyhemoglobin spectrum. Again, the addition of a reducing agent to normal blood speedily changes its spectrum, while this does not happen when one-fourth or more of the coloring matter is combined with CO.

CO, besides its indirect effect on the tissues by interrupting the oxygen-carrying power of the blood, is a direct poison and capable of inducing marked destructive changes. Primarily the heart beats slowly and violently. Rupture of blood-vessels may occur during this stage. Secondly the heart beats rapidly and feebly. This is the period of vasomotor paralysis; and as a result of this condition, bright-red areas may appear on the surface. When not seen until after death, they are generally mistaken for postmortem effusions. However, they may occur in those who ultimately recover. At first there may be abnormal motility, and possibly violent convulsions; later there may be extensive paralysis. In about 70 per cent. of the cases of poisoning with this gas, the urine contains a reducing substance, which in some instances is sugar, in others glycuronic acid. A test for reducing bodies in the urine may serve as an aid to diagnosis in doubtful cases. Albumin also is present in about 20 per cent., and lactic acid appears in severe poisoning.

The degenerations that may result from chronic poisoning with CO are numerous and extensive. The marked and persistent anemia so frequently observed is due in part to the rapid destruction of CO-bearing corpuscles by the liver, and in part to the nephritis that comes from the elimination of the decomposition-products. In dogs chronically poisoned with this gas, the epithelium of the convoluted tubules undergoes necrotic changes and may be stripped off altogether. The enormous increase in nitrogenous metabolism with muscular degeneration reminds one of phosphorus poisoning.

Musso has reported five interesting cases of chronic poisoning; one of them showed progressive weakness, both physically and mentally. There was incoordination of movement, including speech, with repeated epileptiform attacks. Of the five, two slowly recovered, and three passed into a condition of typical paralytic dementia and died. The blood-vessels in various organs were found to have undergone fatty and hyaline degeneration. Koren has reported other cases, in one of which section showed dilatation of the heart consequent upon advanced fatty degeneration of the muscle, serous effusion in the pericardium and the pleural cavities, and an enlarged spleen.

In acute poisoning, the color of the blood is considered pathognomonic. The skin is likely to be stained over limited areas; and the soft tissues, the muscles and viscera, are rose-red. According to Kobert, CO hemoglobin has been detected in the body eighteen months after death. The corpuscles retain their form some time after death, and the arteries are generally full of blood. There are ecchymoses in the meninges and capillary hemorrhages in the brain. Pneumonic changes are frequently observed in the lungs, and fatty changes in the kidney, liver, and heart. Ziemssen found a diphtheric-like exudate on the gums, in the trachea, and in the colon and rectum. Gangrene of the muscles of the neck has been reported. Deep bedsores have been known to form in a very short time.

The Caustic Alkalies.—Locally the caustic alkalies destroy tissue in much the same way as the strong mineral acids. However, there is this difference: the eschar formed by the acids is hard and dry, while that formed by the alkalies is soft and gelatinous. It is the difference between syntonin and alkaline albuminate. Scar-formation and resulting contractions are similar after acids and after alkalies. The penetration of the tissue is also deep, and perforation of the walls of the alimentary canal may occur. Stricture of the esophagus is a frequent result of the local action of the caustic alkalies. The effect of the subcutaneous injection of strong alkalies is influenced to an important degree by the injured part remaining free from bacterial infection or by its becoming infected. In the former instance the necrosis is confined to the muscles, while the blood-vessels remain unaffected and the nutrition of the part continues. The writer saw an example of this a few years ago, when a physician injected strong ammonia in different parts of the body in a case of morphin poisoning. The necrosis of the muscular tissues was extensive around the point of each injection, but the blood-vessels remained intact. On the other hand, when infection happens, the blood-vessels may be closed by thrombi and the nutrition of the part is prevented. The local action of strong alkalies upon nerves results in degenerative changes which are histologically similar to those due to section of the nerve.

Caustic Potash and Soda; Caustic Lye.—After swallowing any of these in concentrated solution, the mucous membrane of the mouth and pharynx is white and swollen, with dissolved or necrotized patches. The mucosa of the stomach is macerated and corroded, exposing the reddened subjacent tissue. There may be perforation. The intestines are highly inflamed. If death be delayed, ulcerations occur along the alimentary canal, and later contractions with stricture of the esophagus may result. Even when the esophagus is not closed, the contractions in the walls of the stomach may be sufficient to reduce materially the size, alter the form, and destroy the function of this organ.

Although the carbonates both of potash and soda have a local caustic action, poisoning is practically limited to the potash compound. This is due to the more markedly depressant action of potash, especially on the vaso-motor center and the heart.

Ammonia.—This poison may be inhaled in the form of gas, or it may be taken into the stomach, dissolved in water or in alcohol. In gaseous form it causes inflammation of the mucous membrane of the nose, mouth, pharynx, larynx, and bronchi. The conjunctiva may also be much inflamed, and prolonged exposure may lead to ophthalmia. The inhalation of ammonia leads to free salivation, and this may be accompanied by nausea and vomiting. A pseudodiphtheric membrane may form in the larynx and lead to great dyspnea. Lehmann found that animals compelled to breathe air containing from two to three parts per thousand of ammonia-gas showed salivation, inflammation of the conjunctiva, dyspnea, and convulsions terminating in death. On section he found edema of the glottis, hemorrhage, and, when death was delayed, purulent bronchitis. Microscopic examination showed some of the alveoli quite normal, others collapsed, and still others emphysematous. The lung-tissue was infiltrated with numerous leukocytes, and, in the hemorrhagic foci, unchanged red corpuscles were seldom seen; but leukocytes were abundant and surrounded by pale-red masses and swollen epithelial cells. In rabbits that died during the experiment, the most constant and prominent lesions consisted of hemorrhagic tracheitis and laryngitis. The tracheal epithelium was extensively destroyed and the cells robbed of their cilia. In the case of one animal that had survived an exposure of four and one-half hours to a $5\frac{1}{2}$:1000 atmosphere, but died during a second experiment, Lehmann found purulent fibrinous pleuritis and pericarditis. He attributes the pleuropericarditis to the action of bacteria which had found their way into the blood through lesions caused by the gas.

When a solution of ammonia is swallowed, the mucous membrane of the mouth and pharynx is swollen, reddened, and destroyed in patches. The stomach contains bloody fluid, and the walls are inflamed and may be perforated. The blood may be dark or light red, but it shows no spectroscopic changes. Fatty degeneration and ecchymoses may be found in the liver, and a glomerulonephritis may be established. The changes in the lungs resemble those observed after inhalation of the gas, but are generally less pronounced.

Caustic Lime.—The lesions induced by caustic lime have not been closely studied, and only general statements can be made. A child that fell into a lime-pit is said to have died almost instantaneously. Others, who ate apples cooked by being placed in unslaked lime, showed evidences of local irritation and had convulsions. An old man is said to have rubbed caustic lime and green soap over his entire body; the epidermis turned brown and was destroyed. Suppurating ulcers may result from external application, and parenchymatous nephritis may develop later. When taken internally, caustic lime corrodes the mucous membrane of the stomach and intestines, the blood becomes thick and cherry-red in color, and the meninges of the brain are hyperemic. When drawn into the lungs, the epiglottis is swollen and the mucous membrane of the trachea and bronchi is corroded and becomes grayish white.

VEGETABLE AND SYNTHETIC POISONS.

The Organic Acids.—**Oxalic Acid.**—This substance in strong solution is an escharotic, but it is poisonous apart from its action as a caustic, inasmuch as the neutral oxalate of potassium may cause death. The insoluble

ble oxalates, such as those of lime and magnesium, are inert. It is now an established fact that the presence of soluble salts of lime in the blood is essential to the phenomenon of coagulation; and both free oxalic acid and the soluble oxalates, by precipitating the lime, prevent coagulation and so alter the composition of the blood that disastrous results follow. At the same time, normal metabolism is interrupted and sugar appears in the urine.

There are those who believe that the condition known as oxaluria, characterized by the continued deposition of crystals of the oxalate of lime in the urine, is a form of chronic poisoning with this acid, which may be introduced from without, especially in certain vegetable foods, or be generated within the body as a result of imperfect oxidation, and that this chronic poisoning is frequently followed by diabetes. However, our knowledge concerning the significance of a continued deposit of oxalate of lime is yet too indefinite to permit the expression of any positive statements.

In acute poisoning with the acid, the mucous membrane of the mouth, esophagus, and duodenum is grayish white and more or less corroded. The mucous membrane of the stomach may escape injury, but generally it is swollen; and close inspection will reveal numerous pin-point hemorrhagic spots. Microscopic examination shows crystals of calcium oxalate in the folds of the mucous membrane. In many instances there is a bloody diarrhea, and octohedral crystals may be found in the discharges. Various crystalline forms—octohedra, dumbbells, plates, and whetstones—may be found in the uriniferous tubules, and on the line between the cortex and medulla these crystals may accumulate in such quantity that the concretions formed may be seen by the unaided eye. The statement formerly made that only dumbbell forms are developed in the kidneys, while the octohedra first crystallize in the bladder, has not been substantiated by more thorough investigation. Convulsions and motor paralysis are among the possible symptoms in acute poisoning with oxalic acid, but the writer has not been able to find any record of study of the central nervous system.

Acetic Acid.—Kobert states that after death there is extensive infiltration of blood under the skin, giving a violet coloration. The tongue and esophagus are white or brownish from the local irritation. The stomach contains a brownish fluid, while the walls are violet or brownish, possibly black. The mucous membrane of the small intestine is thickened and brownish red, while the peritoneum is violet gray.

Carbolic Acid.—In 1882 Kobert collected 169 cases of acute poisoning with carbolic acid, and in 1893 he added about 50 more to the list. In a large number of suicides that recently occurred in Philadelphia and New York, carbolic acid was employed as the agent. Chemically, carbolic acid is, of course, not an acid.

A certain quantity of phenol combines with sulphates and glycuronic acid in the body, and these conjugated acids are eliminated by the kidneys. It is generally stated that phenol is not poisonous until the amount is greater than that which can be taken up by the above-mentioned bodies. In accord with this belief, the clinician at one time was guided in his administration of phenol and kresol by the amount of inorganic sulphate in the urine; and so long as barium chlorid produced in this excretion a precipitate insoluble in hydrochloric acid, it was believed that the danger-line had not been reached. There is undoubtedly some truth in this, inasmuch as the conjugated phenol is much less poisonous than the free body; but it is by no means certain that the conjugated acids are wholly free from deleterious effects, especially on the kidneys.

Concentrated carbolic acid, when applied to the unbroken skin, gives it at first a white, frozen appearance, followed by necrosis. A 5 per cent. solution benumbs the surface, and after long exposure may destroy the cutis and may even cause gangrene. Even a 1 per cent. solution may form an eschar on a mucous membrane. Whatever be the mode of administration, the kidney shows a condition of acute inflammation in this form of poisoning. The urine becomes dark, containing casts and albumin.

Salicylic Acid.—While salicylic intoxication lasting for some days after the discontinuance of this remedy is not infrequently observed, the acid is generally regarded as devoid of any permanently injurious effects. This belief is warranted by the records of medical literature; and yet salicylic acid is capable of doing injury, and in its employment some precaution is desirable. Hesselbach found that when this acid was administered to rabbits by the mouth, in doses of 1.087 gm. per kilo. of body-weight, it caused death without any special symptoms. Section showed ulceration and partial necrosis of the mucosa of the stomach and marked edema of the whole wall. Hypodermic injection of 1.6 gm. per kilo. caused death, the autopsy revealing marked hyperemia of the kidneys, especially of the parenchyma, also of the liver and of the brain. Microscopic examination of the kidney showed hemorrhagic foci in the interstitial tissue and in the tubules. Epithelial changes were found in certain areas, while others seemed normal. Indeed, in some of the tubules, every cell seemed to be altered. The cell contour was often indistinct, the nuclei sometimes protruded, and the lumen was filled with detritus. In many straight tubules the detritus contained numerous blood-corpuscles. Hesselbach believes that the characteristic effect of salicylic acid on the kidneys is to be found in the hemorrhagic condition and not in the epithelial changes. Hemoglobinuria has been reported as a result of salicylic acid intoxication.

Salol.—This substance, which consists of about 40 per cent. of phenol and about 60 per cent. of salicylic acid, and which splits up into these constituents in the body, is generally believed to be free from poisonous properties. However, this cannot be true, if the dissociation actually occurs; and that this does happen, sometimes completely, there can be no doubt. Carbolic acid intoxication has been observed after the administration of excessive quantities of salol. The odor of this drug was plainly perceptible in all the viscera, especially in the brain. The lower intestines were hyperemic and the stomach the seat of catarrhal inflammation. Microscopic examination showed an accumulation of cellular elements in the renal cortex. Most of the glomeruli were abnormal, and many of them were surrounded by a cellular infiltration. The epithelial cells of the convoluted tubules were in a state of cloudy swelling, and some showed fatty degeneration. The contour of the cells was indistinct, and in many the nuclei could not be discerned. The lumen of the convoluted tubules, without exception, was filled with debris. On treating fresh preparations with osmic acid, there appeared in the cortex numerous dark masses with their long diameters in the radial direction of the parenchyma. They consisted of decomposition-products of epithelial cells undergoing fatty changes, and some of them contained large needles of fat. While the masses of detritus in the convoluted tubules were formless and less numerous, in the straight tubules they were cylindric. Cross-section showed that these cylindric masses consisted of a more homogeneous center, surrounded by large masses of cell nuclei. In a few the

periphery contained red blood-corpuscles, some of which were normal, while others were crenated.

Hesselbach concludes from experiments upon animals that poisoning with salol results from the carbolic rather than from the salicylic acid. This would be the reasonable presumption, since phenol is much more poisonous than salicylic acid.

Picric Acid.—Adler reports a case in which the administration of a 1 gm. dose of picrate of potash led to the following condition: There was severe pain in the stomach and bowels; yellow material was vomited, and a diarrhea with ruby-red stools set in. The phalangeal joints of the fingers of both hands were extended, while the metacarpophalangeal joints were closed. The urine was red, acid, and contained neither albumin nor bile-pigments. A blood-count showed the red corpuscles greatly decreased and the white increased. In other cases of poisoning with this substance, erythema has been noted. There may be transient anuria, and in other instances the urine may be albuminous. In animals experimentally poisoned, Rymasz found both the central and the peripheral nerves colored. In the blood, along with broken corpuscles, there may be found red granules, partly free and partly in the white corpuscles, consisting of picramic acid.

Ergot.—At the present time there is no certainty concerning the nature of the active principle or principles of ergot. Kobert has obtained two poisons, sphacelinic acid and cornutin,¹ but not in a state of chemical purity. To the first he attributes the gangrenous changes of ergotism; while the other, he believes, induces the convulsive form that is so pronounced in certain epidemics. More recently Jacobi has obtained a chemically pure body to which he has given the name sphacelotoxin, and which he believes to be the active principle of Kobert's sphacelinic acid. However, the chemistry of ergot remains largely undetermined.

Chronic ergotism manifests itself in two forms: (1) convulsive or spasmodic ergotism, and (2) gangrenous ergotism.

The convulsive form usually begins with gastro-intestinal and vasomotor disturbances. Loss of appetite, nausea, vomiting, diarrhea, cyanosis, formication, muscular weakness, and feebleness of the heart's action are the symptoms. After these have continued for a variable time, symptoms more distinctly nervous occur. Specks are seen floating before the eyes, ringing noises are heard, and irritation of the skin becomes constant. Mental perception becomes dull, and an epileptic condition with the usual hebétude appears. Convulsive seizures become frequent. The flexors overcome the extensors; the hands are bent on the wrists, and the fingers are partly closed. Permanent contractions result. The tendon reflex is soon lost, and the condition resembles that of tabes dorsalis. There may be stupor and acute dementia or melan-cholia.

In gangrenous ergotism an erysipelatous redness spreads over the toes and fingers, and gangrene sets in. One or more phalanges of the toes or fingers, the feet or the hands, the legs or the arms, may become necrotic and fall off. The external genitals may be involved in these necrotic changes, and gangrenous areas may appear on the skin of any part of the body or in the intestinal mucous membrane.

Grünfeld fed animals with sphacelinic acid. In cocks, gangrene soon appeared in the comb, then in the wattles, tongue, wings, and crop. Hogs lost their ears, and horses and cows their tails, ears, and hoofs. When applied locally in concentrated form, sphacelinic acid caused gangrene of the tissue with which it was in contact.

Grigorjeff submitted animals to chronic poisoning with ergot, and found the following conditions: In the central nervous system the most important changes were localized in the posterior columns (especially those of Burdach) of the cord, extending throughout these and showing the characteristics of a recent myelitis. The alterations consisted of vascular hyperemia, dilatation

¹ Since Kobert's ergotinic acid is inert when given by the mouth, although markedly toxic when administered subcutaneously or intravenously, it cannot be concerned in the causation of epidemic ergotism.

of the perivascular spaces, cell-infiltration often found in colonies, edema of the supporting tissue, and degeneration of the nerve-fibers. In the perivascular spaces, granular cells were frequently found. The degeneration of the nerve-fibers was rendered evident by swelling and granulation of the axis-cylinder and partial disintegration of the myelin sheath. The endothelium of the capillaries was fatty. The other parts of the white and the gray matter of the cord, also the brain, displayed the appearance of passive hyperemia with edema of the neuroglia. In all regions of the cord and the brain cortex there were observed circumscribed collections of blood-corpuscles here and there in the vicinity of the blood-vessels. In a few animals some of the ganglion-cells of the anterior horns of the cord were somewhat swollen and granular. In all there were degenerative changes in the fibers of the posterior roots.

Of other organs, the liver and the kidneys were most markedly affected. In these the changes involved not only the special secreting cells, but the vessels also, and were of an atrophic and degenerative character. In some animals only a few cells relatively were altered, and the changes were not marked; while in others the involved areas were more extensive and the process more advanced. In all the affected animals the cells of the parenchyma of the liver and kidney showed granular degeneration, with less frequent destruction of the nuclei. Fatty changes of the epithelial cells of the kidneys were observed in localized areas. Where the granular degeneration was advanced, it was accompanied by vacuolization of the cell-protoplasm and chromatolysis of the nuclei. The degeneration in the kidney affected principally the convoluted tubules. Hand in hand with the degenerative changes, desquamation of epithelium and the formation of granular casts in the lumen occurred. In the vessels of the liver and kidney, which were distended with blood, degenerative cellular changes were limited to the capillaries, the endothelial cells of which were granular and fatty; rarely the nuclei were destroyed. There was desquamation of the endothelial cells, and the resulting detritus formed finely granular masses. This led to irregular distention of the vessels. Drops of fat were observed in the capillaries, and these were sometimes so massed as to fill the lumen. Sometimes blood-extravasations were found in the capsules of Bowman and in the tubules. Small aggregations of granulation-cells were observed in the interstitial connective tissue in one animal. Along with the above-mentioned degenerative changes in the parenchymatous cells of the liver and kidney, regenerative processes were observed, as shown by the presence of karyokinesis. This was seen more frequently in the endothelial than in the parenchymatous cells. The configuration varied from the normal, inasmuch as the chromatin segments were irregularly divided. Many cells showed both karyokinetic and fatty changes at the same time.

In all the animals, changes were found in the alimentary canal. These were of a catarrhal nature and generally localized in the lower portion of the ileum. In some cases, circumscribed blood-extravasations were observed in the vicinity of the vessels in the mucous membrane.

The changes in the lungs consisted in part of hyperemia and hemorrhages, and in part of involvement of the capillaries. The tissue in the vicinity of the extravasations showed inflammatory phenomena, such as swelling and desquamation of the alveolar epithelium and infiltration of the septa with lymphoid cells. In some of the animals, inflammatory processes

were observed in the bronchioles. The endothelial cells of the capillaries showed changes similar to those observed in the liver and kidney. Fatty emboli were also seen in some capillaries. Very rarely was mitosis observed here.

The heart muscles were atrophied, the transverse striation was lost, and some of the fibers were granular. There was hyperemia, and the endothelial cells of some of the capillaries showed cloudy swelling, granular and fatty changes.

The voluntary muscles and the spleen showed no changes other than hyperemia and atrophy.

In the combs of cocks the alterations were due to occlusion of the blood-vessels with agglutinated red corpuscles and hyaline thrombi. As results of this condition there were edema of the supporting tissue, with emigration of leukocytes from the occluded vessels, and gradual but complete necrosis of the portion deprived of blood-supply. A finely granular pigment was found in the supporting tissue, which probably has its origin in the blood-coloring matter.

The white corpuscles of the blood were increased, while the red were diminished. In cocks the hepatic capillaries were sometimes found containing red corpuscles which had lost their nuclei and were agglutinated into homogeneous masses. Hemosiderin granules were found in some of the capillaries, both in the white corpuscles and in the endothelial cells.

Winogradow studied the pathologic histology of chronic ergotism in the epidemic of 1889 in Russia. The chief changes consisted of hyaline degeneration of the walls of the capillaries, occlusion of the lumen partly with blood-coagula and partly with hyaline masses, and coagulation-necrosis of the parenchymatous elements with proliferation of connective tissue. In the spleen he found necrosis of the Malpighian bodies, and in the kidneys deposits of smooth, glistening masses in Bowman's capsules, with secondary compression of the glomeruli, leading to their complete obliteration.

Morphin.—Although opium contains a large number of alkaloids, morphin is its most active principle and the only one that needs consideration in an article on intoxications. According to Clautrian, morphin and narcotin are the only alkaloids that exist preformed in the plant, the others resulting from fermentative processes in the juice of the poppy during the drying.

Binz thinks that the action of morphin, as well as that of chloroform, is due to a cloudy change or slight coagulation in the substance of the brain. That the chief effect is on the central nervous system must be admitted, but at the same time it must be confessed that neither the histologist nor the chemist has been able to explain in any satisfactory way the mode of action of this poison. Indeed, there is no consensus of opinion concerning its effect upon the circulation in the brain. The most trustworthy experiments indicate, however, that in morphin narcosis the cortex of the brain, at least, is anemic.

A small part of the morphin administered is eliminated in the urine, while the greater part passes out through the bowels. This is true, whether it has been taken by the mouth, hypodermically, or intravenously. This fact is of practical importance for two reasons. It explains why so small a portion of the drug can be recovered from the urine, and it shows the importance of washing out the stomach in morphin poisoning, even when it has been administered subcutaneously. In cases of poisoning, morphin, oxydimorphin, lactic acid, albumin, sugar, and other reducing substances

may be found in the urine. Morphin may also be eliminated in the secretion of the mammary glands, and nurslings have been poisoned in this way. In acute poisoning, death results from failure of respiration and progressive edema of the lungs. This is due to paralysis of the medulla oblongata.

The autopsy findings are not constant nor characteristic. Indeed, cases of unquestionable morphin poisoning are recorded in which the most careful search has failed to reveal any abnormality. Usually, however, the meninges are congested and the cavities of the brain contain an abnormal quantity of cerebrospinal fluid. The lungs are congested and edematous. The blood is dark and fluid, and the bladder is frequently distended. Rarely the abdominal viscera are greatly engorged and ecchymoses are found in the mucous membrane of the stomach. The pupils may be contracted, but no great reliance can be placed on this condition, as they are sometimes quite dilated.

On section after chronic poisoning, the skin is found to be cirrhotic, the muscles atrophied, and the viscera anemic. The brain is edematous; and in animals experimentally poisoned, degenerative changes have been found in the posterior columns of the cord.

Chloral Hydrate.—Locally applied, chloral is a strong irritant; and, when taken in an unsuitable vehicle, it may cause inflammation, hemorrhage, and destruction of the mucous membrane of the esophagus and stomach. Desquamation of the epidermis has been known to follow single doses, and the so-called chloral rash is not infrequently observed. In those chronically addicted to the use of this narcotic, the gums are frequently swollen, the tongue may be blistered, and pustules may form in the skin. In rare instances ulcers form at the base of the nails, and the hair falls out.

Bornträger has collected the literature of forty-four cases of chloral poisoning, and from his studies the following statements concerning the post-mortem findings are chiefly gleaned: Chloral is slightly antiseptic, and it is said that postmortem rigor is somewhat delayed after poisoning with it. However, this is not marked and there may be many exceptions to the rule. Rigor is marked, and it is believed from some animal experiments that chloral coagulates myosin. However, since these experiments were made upon frogs, and since the amount of the poison employed was relatively large compared with the minimum or even the average fatal dose in man, too much must not be inferred from results thus obtained. Subcutaneous effusions of fluid blood are common and are identical with those seen after fatal chloroform anesthesia. The pupils are dilated moderately, sometimes widely. The blood is generally fluid, although this is not so constantly the case as after chloroform. The condition of the heart is variable, with dilatation in the majority of instances. In chronic chloralism, microscopic examination of the muscle of the heart demonstrates the existence of fatty changes. The lungs are hyperemic, sometimes edematous, and marginal emphysema has been observed. The abdominal viscera are engorged with blood, and hemorrhagic spots may be found. The occurrence of ulceration in the stomach has already been mentioned. The meninges are hyperemic, and the brain itself may be either congested or anemic. The urine is sometimes clear and pale, at other times colored with blood.

Sulfonal.—About fifteen cases of chronic poisoning with this drug have been reported. The most constant symptoms consist of the vomiting of a greenish mucus, pain in the abdomen, general weakness, and death from paralysis of the heart. Petechial and pustular eruptions were observed in some cases. The urine contains various coloring matters—hemoglobin, methemoglobin, hematoporphyrin, and bile-pigment. It may or may not contain albumin. According to the researches of W. J. Smith, sulfonal is eliminated for the greater part in the form of ethylsulphonic acid. I have not been able to find any record of the findings at autopsy.

Chloroform.—That chloroform is a cellular poison when used in excess is demonstrated by its frequent application in vapor form for the purpose of killing bacteria, when it is desired to alter the protoplasm of these cells as little as possible. Locally it irritates, stimulates, and then paralyzes. It arrests the ameboid movements of leukocytes and of other low forms of animal life. It coagulates protoplasm; but we can hardly accept the theory of Binz, that its narcotic effects are due to a slight and transient coagulation of the protoplasm of the nerve-cells. The lecithin of nervous tissue is believed to absorb chloroform. It forms a chemical compound with hemoglobin, according to Schmiedeberg, and the corpuscles are capable of taking up large quantities of it. However, under its prolonged action the corpuscles break down. Formed elements in the blood are not essential to the narcotic action of chloroform, because frogs the blood of which has been replaced by saline solution may be anesthetized with it. It benumbs both the gray and the white matter of the brain, and diminishes blood-pressure. The manner in which it kills, whether through paralysis of respiration or of circulation, has been a matter of considerable discussion and experimentation and cannot be dwelt upon here.

The condition of the body after death from chloroform is a matter of both scientific and practical interest. Some have placed much stress upon the intensity and continuance of rigor; but the studies of Bornträger have shown that rigor after death from chloroform is very variable, both in time and in degree. Postmortem subcutaneous effusions are common on account of the fluid condition of the blood, but are not characteristic in appearance. Drops of chloroform on the face may leave significant marks, and the direct effects of the vapor on the eyes may be recognized by redness of the conjunctivæ and edema of the lids. The pupils are generally moderately dilated, but this condition exists in death from many other causes.

The frequency with which air-bubbles are found in the blood after death from chloroform has been the subject of some discussion. As early as 1848, Virchow observed air in the blood after chloroform poisoning. Since that time others have confirmed this observation, and some have gone so far as to claim that air in the blood, except under other explainable conditions, is characteristic of chloroform poisoning. On the other hand, Kappeler has claimed that gas is not found in the blood after chloroform more frequently than after death from other causes. Binz thinks that in the heavy breathing of anesthesia, accompanied as it frequently is by vomiting, by an accumulation of mucus in the throat, and by the unfavorable position often taken by the tongue, air may be forced through the unbroken walls of the air-cells and into the blood. Ewald and Kobert support this view. In this connection Bornträger calls attention to a case in which marked emphysema of the tissues of the neck resulted from the forced respiration employed in morphin poisoning. In 34 out of 41 cases Senator reports the heart shrivelled, flabby, and with its cavities empty at the time when the other muscles of the body were in rigor. Casper regarded this condition as characteristic and designated it as the "chloroform heart," but others do not consider it pathognomonic. However, in a collective investigation of deaths from chloroform, Bornträger finds the above-mentioned condition of the heart to be very frequent. Sometimes all the cavities are empty, sometimes the ventricles are empty while the auricles are filled with fluid blood, and again only one ventricle may be empty. W. Koch found the left heart

generally empty, while the right heart and the veins were full. In 53 cases which Kappeler reports, the right heart contained much blood in 16, all the cavities were full in 6, and all empty in 7. It will be seen that there is no constancy in this condition. No characteristic change has been observed in the lungs. Edema and hyperemia are the most frequent abnormalities. According to Bornträger, subpleural effusion is also common. The mucous membrane of the bronchi is sometimes normal, while in other instances it shows the characteristics of asphyxiation, redness, and hemorrhagic spots. Most of the abdominal organs are congested. The portal vein and the inferior cava are full of blood. Hemorrhages are frequently found, especially in the stomach, spleen, and kidneys. Initial parenchymatous degeneration is observed in various organs when death does not occur until after five or six hours. In dogs subjected to prolonged anesthesia, Strassmann found fatty changes in the heart and liver. The meninges and sinuses of the brain are rich in blood. In 24 cases, according to Bornträger, the brain was reported to be hyperemic and edematous in 8, pale in 6, while in others nothing is stated concerning the condition of this organ.

Alcohol.—The excessive use of alcoholic beverages leads to pathologic changes in most of the tissues of the body. The ill effects of such drinks are frequently attributed to adulterations; but with possibly some few exceptions, the most deadly constituent of alcoholic beverages is the alcohol itself. In its effect on man, amylie alcohol differs from ethylic only in degree and not in kind. The former is the more poisonous, but the pathologic lesions induced are the same in kind, whether the beverage contains a fraction per cent. of amylie alcohol or contains only ethylic.

Alcohol has both a local and a systemic action. The local effect depends upon the concentration, while the systemic is more dependent upon the absolute amount taken and is quite independent of the extent of dilution. Strong alcohol irritates, inflames, and, if the concentration be great enough, may corrode tissue. It absorbs water and destroys the vitality of the cell.

The proportion of alcohol in the blood in the most profound narcosis of drunkenness is considerably less than 1 per cent., but no one knows to what extent it may accumulate in various organs. It is eliminated from the lungs and through the kidneys, but the greater part of it is consumed in the body, the amount eliminated unchanged being only about 5 per cent. of that taken. However, this is subject to considerable variation according to the individual and his condition at the time.

The pathology of alcoholic intoxication can be studied in the living inebriate, in his body after death, and too frequently in his children.

Some of the pathologic conditions that are more or less prominent during life are the following: Acne rosacea often prominently obtrudes itself. There is a tendency to the formation of pustules and furuncles, in some instances resulting probably from penetration of the diseased cutis by the pyogenic germs so constantly present on the surface. Catarrhal conditions, although not confined to alcoholics, are very common among them. The mucous membrane of the nose, pharynx, Eustachian tubes, and stomach is frequently involved. Atheromatous degeneration of the blood-vessels, hypertrophy and dilatation of the heart, and venous stasis are often easily recognizable. Changes in the liver and kidneys cause dropsical accumulations. Changes in the nervous system are indicated by tremor, paralysis, anesthesia, melancholia, and dementia.

When death results from a single debauch in a person not previously a hard drinker, pathologic lesions are not marked. Hyperemia of the brain is the most constant condition. When the alcohol has been taken in con-

centrated form, there may be a high-grade inflammation of the mucous membrane of the alimentary canal, with multiple ecchymoses. There may be edema of the lungs. The odor of alcohol is perceptible in all the viscera and in the muscles.

The findings after death from chronic alcoholism are subject to considerable variation within certain limits. This is doubtless due to the fact that in most instances the use of the poison has been continued through years, during which time the different individuals have lived under widely varying concurrent conditions. In general, the macroscopic changes are as follows: The mucous membrane of the stomach is hyperemic, and the organ contains an excess of thick, tenacious mucus. Ulceration may be present. Changes in the intestines are usually not marked, although there may be some thickening of the membrane and possibly edema.

Alcohol is regarded as the most frequent cause of cirrhosis of the liver, and any one of the forms of this affection may be found in chronic alcoholics.

Frequently a cirrhotic condition is found in the kidneys; but this is by no means constant, and there are those of wide experience who deny that structural changes in this organ are found more frequently in alcoholics than in others. Formad believed that the "pig-backed" kidney was characteristic of chronic alcoholism. The lungs are not the seat of any constant or uniform lesion. The muscle of the heart often appears unusually yellowish and contains an excess of fat. The dura and pia are frequently hyperemic, and the brain may be edematous.

The microscopic pathology of alcoholism has been studied both in man and in the lower animals. Fatty changes are most frequently observed. These are most marked in the liver and the brain, and this is supposed to indicate that the alcohol accumulates in these organs. Both the liver-cells and the so-called cells of Kupffer are involved. The entire protoplasm of the cells may be filled with drops or globules of fat, of variable size. The fatty changes are not uniform, at least in degree, throughout the organ, but are most marked about the portal veins, in the periphery of the lobules, and decrease toward the center. The intensity of the fatty changes varies with the length of time during which the poisoning has continued, and in animals it is increased by the addition of amylic alcohol to the spirit. In some instances the epithelial cells of the gall-ducts contain globules of fat. The nerve-cells of the brain also show fatty changes. The extent to which fatty changes are found in these cells is very variable. In the milder cases the globules are seen only in the periphery, while in more advanced stages the entire cell-protoplasm may be fatty in the highest degree. The nuclei of these cells stain imperfectly, and in some instances seem to be quite disintegrated; the nerve-cell processes are also profoundly altered (Berkley). The walls of the cerebral vessels may contain fat deposited in the connective tissue of the adventitia and in the endothelial cells. Localized fatty changes of the epithelial cells of the convoluted tubules of the kidney may be observed, but the changes are not so extensive as they are in the liver.

In the stomach, the existence of a true glandular gastritis is confirmed by the microscope. The peptic glands are found to be fatty and even necrotic, the chief cells being more extensively involved than the parietal. The spleen and lymphatic glands are infiltrated with corpuseles containing fat.

There is also a granular parenchymatous degeneration in various organs. The nerve-cells of the brain often show this condition to a marked degree,

with vacuolization. This granular degeneration may be marked in the liver; and, like the fatty, it is most marked in the immediate vicinity of branches of the portal vein, where the poison acts in the most concentrated form. Here whitish spots may be seen, and the cells within these areas may exist in a condition of more or less marked coagulation-necrosis. The increase in the connective tissue is easily recognizable.

Lymph-stasis is observable in different organs, especially in the stomach, liver, and brain. Whether this is due to the feebleness of the circulation of the blood on account of the condition of the heart or to nervous disturbances is an undetermined question. The perivascular spaces of the hepatic capillaries may be greatly distended. In the stomach and intestines the submucosa may be very edematous.

Experiments upon animals seem to indicate that the liver-cells may, on the discontinuance of the use of the poison, recover even after marked fatty changes have taken place.

Some Rare Vegetable Poisons.—Abrin and Ricin.—These interesting poisons have attracted much attention on account of their resemblance to bacterial toxins and the venoms of serpents. They are albuminous substances, and in their action bear some resemblance to ferments. Abrin is contained in the jequirity bean, while ricin is the poisonous constituent of the castor bean. They have not been obtained in a state of chemical purity, and were believed by their discoverer, Kobert, to be identical until Ehrlich showed that an animal rendered immune to one is still susceptible to the action of the other. Kobert thinks that their poisonous effects are due to the coagulation of the blood. Not only do they cause the natural blood to coagulate, but, if one of them be added to blood from which all the fibrin has been removed, a new coagulation results, or at least a precipitate forms. This precipitate, according to Kobert, is very similar to, but not identical with, fibrin. Both the corpuscles and the serum obtained from defibrinated blood coagulate on the addition of abrin or ricin. If the corpuscles be repeatedly washed in a centrifuge, and even if all the coloring matter be removed, the stroma shaken in water with abrin or ricin still coagulates.

When administered by the mouth, these substances are much less poisonous than when administered hypodermically. This, which is known to be true of certain venoms also, is explained by supposing that a portion is digested and thus deprived of its poisonous properties. That which is absorbed coagulates the blood in the vessels in the walls of the intestines as soon as it reaches it, a small thrombus is formed, and ulceration results from self-digestion. This is the explanation of the action of these substances, as taught by Kobert. He claims that they are not local irritants, and that all the lesions resulting from poisoning with them are due to their power of coagulating the blood.

The pathology of toxalbumin intoxication as seen in the effects of ricin and abrin has been carefully studied by Flexner, who lays special stress on the occurrence of focal necroses.

Werhovsky has made a valuable contribution to the pathologic anatomy of abrin poisoning. He finds most marked macroscopic changes in the intestines. The peritoneal cavity contains more or less serous fluid. Both the parietal and the visceral layers of the peritoneum are injected, and the large and small intestines contain liquid colored with blood. The mucous membrane of the stomach and intestine is covered with a grayish-white coating; Peyer's patches and the peritoneal lymph-glands are enlarged. The liver and kidneys are swollen and filled with blood. The pericardium

contains a bloody transudate and shows hemorrhagic spots, and both ventricles are greatly dilated and filled with partially coagulated blood. The spleen is enlarged and the lungs are edematous.

Microscopically changes are found to be rather extensive in various organs, but those in the heart and in the digestive organs are believed to be the most significant. The microscopic appearance of the walls of the heart seems to be most characteristic. A transverse section of the fibers shows dark and light spots. The dark cells consist of unchanged muscle-fibers, while the light ones are fibers infiltrated with a light-colored fluid. This dropsical condition of the fibers of the muscles of the heart is believed to be the most unique and characteristic finding. Here and there may be observed swollen fibers, the protoplasm of which is uniformly permeated with drops of fat. All the microscopic findings are believed to be due to a venous stasis. This explanation also suffices for the minute hemorrhagic areas in the lungs, liver, spleen, stomach, intestine, and kidney. Degenerative and inflammatory processes are not prominent.

Werhovsky believes that the cause of death in abrin poisoning is to be found in the above-described changes in the heart. They consist of a characteristic dropsical degeneration in which the involved cells swell to twice their normal size. Simultaneously there may be fatty changes.

Phallin.—This is a poisonous albuminous substance, a so-called toxalbumin, found in different varieties of the fungus *Amanita*. According to Kobert, poisoning with this fungus is not rare in Germany and in the Baltic provinces of Russia. About 75 per cent. of the cases terminate fatally. This fungus is mistaken for edible mushrooms. Kobert states that the poisonous action of phallin is due to coagulation of the blood and solution of the corpuscles. Section shows multiple hemorrhages, especially in the liver and intestinal mucous membrane, also subpleural and intraperitoneal. There is inflammation of the stomach, with partial gangrene and destruction of the glands. There are fatty changes in the liver, heart, tongue, and diaphragm. The urine is brownish and albuminous. The meninges are hyperemic.

If a half-milligram of phallin for each kilogram of body-weight be injected intravenously in a dog, cat, or rabbit, and some blood be drawn from the animal half an hour later, the serum which forms will be reddish. If urine be passed about this time, it will be brownish. Later hemoglobin, methemoglobin, and bile-pigments may be found in the urine. There is also a colored substance which appears to be intermediate between hemoglobin and bile-pigment and closely resembles hematin. After death the uriniferous tubules may contain blood-detritus.

Helvellic Acid.—This is the active constituent of the fungus *Lorchel* (*Helvella*), and disappears when the fungus is dried. The symptoms are similar to those induced by phallin. Section reveals dissolved hemoglobin in the cavities of the body. The kidneys are swollen and the tubules contain hemoglobin in crystals and in small round masses, the so-called "blood-drops" of Bostroem. The spleen contains much hemoglobin. Multiple hemorrhages and fatty changes are observed in the liver.

Saponin Bodies.—About 150 plants belonging to 30 families contain saponin substances. Kobert states that no other poison is found so widely distributed in the vegetable world. The aqueous solutions of the saponins lather like soap. When inhaled they induce sneezing, and on being injected subcutaneously they give rise to aseptic suppuration. They act upon the red blood-corpuscles in much the same way as phallin and helvellic acid act. A few instances of poisoning from bread containing corn-cockle have been reported, due to the presence of a saponin body. Lehmann states that bread containing from three to five grams of corn-cockle is harmful.

As was shown by Przybysaewski in 1876, saponin locally applied dilates the blood-vessels, causes stasis, and alters the corpuscles. This may be demonstrated on the web of a frog's foot. The web is properly placed under the microscope, and the position

of the body is so arranged that stasis will not result therefrom. Then the tissue is pencilled with a 10 per cent. solution of saponin. There is a short period of contraction of the capillaries, then they slightly dilate, and the circulation in the part becomes slow. After ten minutes there is complete stasis, at first in the capillaries, later in the small arteries and veins. The white corpuscles cling to the walls, and thus narrow the lumen and lead to complete arrest of the flow. At the same time the heart continues to beat normally; the stasis is thus the result of the local condition. The red corpuscles become pale and their nuclei show more distinctly. Some of the white corpuscles pass through the walls of the vessels and may be seen on the outside singly and in groups.

The effect of saponin on the red corpuscles can be shown by placing a drop of blood and a drop of 10 per cent. solution of saponin side by side on a glass slide and watching the effects as the two fluids come in contact. If the attention be fixed upon a single corpuscle, it will be seen to swell, the central depression disappears, the color fades, fissures appear along the border, and finally there remains only a small granular body.

When a solution of saponin is injected into a muscle, changes take place and lead to the disappearance of the transverse striation, and finally the tissue loses all its structural appearance.

Phloridzin.—This substance is of interest because it induces a diabetic condition in animals. It is a glucosid and is obtained from the cortex of the roots of certain fruit-trees, such as the apple and cherry. According to the studies of Trambusti and Nesti, the chief lesions induced by this substance are found in the kidneys. The convoluted tubules were found to be constantly altered, the change consisting of necrosis of the epithelial elements, with all the characteristics of Weigert's coagulation-necrosis. The lesions varied in degree in different areas. In the initial stages the cells were found swollen and granular, while the nuclei stained well. In more advanced stages the cells had lost their normal form, and the nuclei failed to stain. Still later only detritus remained, with some chromatin granules. Some of the tubules were filled with this débris. The conclusion from these studies is, that, in experimental phloridzin diabetes in the dog, anatomic alterations in the kidney identical with those observed in true diabetes are found.

The glycosuria following its administration is attributed to the loss of power on the part of the kidney to retain the sugar in the blood.

Nitrobenzol.—The employment of various nitro-compounds in the arts has led to frequent poisoning with the same. However, as the pathology of these poisons has not been closely studied, but little information on this subject can be given at the present time. In man, after poisoning with nitrobenzol, the entire surface and the visible mucous membranes have a lead-gray appearance, but the body after death shows nothing characteristic. Rigor mortis is said to be unusually marked, but this is so variable that no great importance can be attached to it. The odor of the poison is usually perceptible in all the viscera. The stomach and the small intestines are congested and may show numerous ecchymoses. Minute blood-extravasations may also be found in the pleura and in the pericardium. The blood is fluid and dark. When diluted with water and examined spectroscopically, it shows the so-called Filchne's nitrobenzol spectrum. The lines of this spectrum resemble those of acid hematin, but lie slightly to the right. Microscopic examination shows the detritus of broken corpuscles. A peculiar brown pigment is formed in the blood, and to this the above-mentioned spectrum is supposed to be due. This pigment is also found in the urine. In experiments on animals, Rohl found the epithelium of the convoluted tubules stained with this pigment. The kidneys at the same time showed epithelial desquamation with granular cloudiness of the cells. The pigment

could not be found in Henle's loops or in the straight tubes. The brain and its membrane were hyperemic.

Schroder and Strassmann have reported cases of poisoning with metadinitrobenzol and have studied the effects of the same poison on animals. Their work is, however, not complete, and leaves us still in need of more exact information. They report that the mucous membrane of the mouth and throat seems to be covered with a fine yellow powder, which cannot be washed away. The skin is a dirty yellowish brown, the sclera yellow, and the lips blue. The urine is clear and dark brown. The stomach contains colored mucus, and the intestinal follicles are swollen. Microscopic examination of the viscera showed nothing of importance. Fatty changes in the liver have been observed after poisoning with orthodinitrophenol.

Nitroglycerin.—After death from this poison, section shows inflammation and fine hemorrhages in the mucous membrane of the stomach and intestines. The brain is congested, and bloody serum may be found in the cavities. No minute study of the lesions induced by this substance has been made.

Amyl Nitrite.—H. C. Wood discovered the fact that amyl nitrite has a destructive action on the blood-corpuscles, and subsequent studies have shown that methemoglobin is formed. In animals experimentally poisoned with amyl nitrite, section shows a congested condition of all the abdominal viscera. The peritoneal and pleural cavities contain serous fluid stained with the altered blood-pigment.

Nitrites.—Nitrous acid and its salts are poisonous, the effects being the same in kind as those of nitroglycerin and amyl nitrite, but less marked in degree. The nitrites irritate the stomach, dilate the blood-vessels, and convert hemoglobin into methemoglobin. All substances forming methemoglobin cause dilatation of the vessels in all organs. A third symptom accompanying these is a fall in blood-pressure; but it is more correct to say that the diminished pressure is due to the dilatation of the vessels. Binz believes that the other effects are secondary to the reducing action of the poison on the oxyhemoglobin. Collischorm has reported two cases of poisoning with sodium nitrite. The most marked effects were diarrhea, marked cyanosis, and the appearance of an exanthem resembling measles. Bacteria may reduce nitrates to nitrites, but it is questionable whether this reduction ever occurs in the alimentary canal of man.

Cases of poisoning among those engaged in the preparation of **melinite**, an explosive used by the French, have been reported, and are believed to be due to the vapors of nitrous acid. The composition of this substance is, however, not definitely known, except to the manufacturers. Kobert states that carbolic and nitric acids are mixed in its preparation, while others state that it is composed of picric acid, gun-cotton, and gum-Arabic. At any rate, it contains a nitro-body.

Dinitronaphthol, known as Martin's yellow, and dinitrocresol, are employed as artificial coloring agents. Both have a reducing action on the blood; and, according to Kobert, at least one death has been due to dinitronaphthol.

Anilin.—This substance, now so largely employed in the arts, is also a methemoglobin producer. Section shows, after death from anilin, besides the blood-changes, a condition of venous dilatation and possibly blood-extravasations. Multiple capillary thromboses have been reported, but are not always found.

Antifebrin or **acetanilid** has practically the same action as anilin, and its frequent employment as an antipyretic agent in fevers is probably responsible for some deaths attributed to the disease. The same is true of antipyrin, phenacetin, antiseptin, kairin, and other coal-tar derivatives.

ANIMAL POISONS.

The Venoms of Snakes.—Some years ago Mitchell and Reichert made a careful study of the venoms of various serpents, such as cobra, rattlesnake, moccasin, and Indian viper, and succeeded in isolating two proteid constituents: one belonging to the class of globulins, and the other to the peptones. Numerous investigators have practically confirmed this work. However, there are some reasons for believing that the poison classed by Mitchell and Reichert among the peptones is, more properly speaking, an albumin. The poisonous globulin, although present in smaller quantities than the peptone, induces the same remarkable effects locally when injected as are seen after snakebite or after injection of the whole venom. Necrosis of tissue results, the capillaries are corroded, local hemorrhage occurs, and the coagulability of the blood is destroyed. The globulin has not only a local action, but may have a paralyzing effect on the peripheral ends of the splanchnics, on the vasomotor center, and on the heart. Feoktistow found that the poisonous globulin paralyzed the respiration, after which the heart beat feebly for a few moments, but not with force enough to carry the blood into the vessels. He found profuse blood-extravasations in all the organs of the abdomen and thorax. The pericardium was often filled with blood, and hemorrhage into the intestines was sometimes observed. The urine also contained blood.

The venom peptone from the rattlesnake causes an edematous swelling about the point of injection. The subcutaneous tissue becomes infiltrated with serum and rapidly breaks down, forming an extensive slough.

In one bitten by a poisonous snake, the parts above the wound soon become blue and swollen, the swelling rapidly involving the whole of the injured extremity and even extending to the trunk. The swollen parts become dotted with petechiæ. The local effects may gradually disappear and recovery slowly follow. In fatal cases, the heart beats feebly, there is great dyspnea, and convulsions at times occur.

Section shows the serous infiltration already mentioned. The serous membranes generally exhibit numerous hemorrhagic spots. The lungs are hyperemic, frequently edematous. The mucous membrane of the stomach and intestines is often dotted with ecchymoses, and the intestines may contain considerable blood. Focal necrosis occurs. The blood in the larger vessels is dark and fluid. Bacteria speedily find their way from the intestines into the tissue, and putrefactive changes rapidly progress.

The blood of many nonpoisonous snakes, as the common garter-snake, is poisonous when injected intra-abdominally into guinea-pigs in quantities of 1.5 c.c. The symptoms and postmortem appearances thus induced resemble those caused by the bite of a venomous serpent.

Immunity to the venom of snakes is rapidly acquired by many animals, as was first shown by Sewall; and animals thus immunized furnish, as Fraser and Calmette have shown, an antitoxin which is successfully employed in the treatment of snakebite.

The uncooked blood of the common river-eel, the Conger eel, and the murena is quite poisonous. Mosso calls the active principle ichthyotoxicum. When applied to the tongue, it burns like phosphorus; subcutaneously it causes marked local reaction.

Fish Poisoning.—Some fish, such as *Trachinus draco*, are supplied with

poisonous glands connected with barbs. Sometimes bathers and fishermen are wounded with these barbs, and fatal results may follow. Locally there is edema, which may be followed by gangrene.

Kakke, a disease prevalent in Japan and other countries along the eastern coast of Asia, is believed by Miura to be due to the eating of fish belonging to the Scombridae.

According to Remy, there are twelve species of tetrodon the ovaries of which are poisonous, and Tahara reports that he has isolated two poisons from the roe: one, a crystalline body, he names tetrodonin; the other, a white waxy substance, he calls tetrodonic acid.

Fish poisoning so frequently observed in the West Indies is believed to be due to the fact that the fish feed upon decomposing medusæ and corals. The symptoms are those of gastro-intestinal irritation.

Fish may be infected with pathogenic bacteria; and these or their chemical products, when taken by man in his food, may prove deleterious. Recent studies indicate that the Russian epidemics of fish poisoning originate in this way.

In our own country, poisoning with canned fish is the most frequent form of ichthyotoxism. This is due to the growth of toxicogenic bacteria in this article of food.

Poisonous Toads.—All toads have poisonous glands, which are seen in the form of warty excrescences on the surface. One of the active agents in the secretion of these glands is phrynin, which, when applied to the mucous membranes of man and other mammals, causes a severe local irritation. Applied to the eye, it causes great pain followed by conjunctivitis and keratitis. Taken internally it acts as an irritant, and when injected intravenously it has a digitalin-like action. Kobert ascertained that toads into which a solution of barium chlorid is injected empty all their poisonous glands, covering the body with a cream-like substance. It is stated that the Indians of New Granada employ the secretion of a pelobate as an arrow-poison, and that deer wounded with the arrows die within four minutes, and jaguars within eight minutes.

Poisonous Salamanders.—The active agent of the poisonous secretion of this animal is an alkaloidal body known as salamandrin. It acts as a local irritant and may induce convulsions similar to those of strychnin. Two milligrams injected intravenously suffice to kill a dog. A hypodermic injection of muscarin causes the salamander to secrete an abundance of this poison. The secretion of the water salamander is less poisonous than that of the fire salamander; but it also may cause severe local inflammation, especially when applied to the eye.

Poisonous Scorpions.—The posterior segment of this animal is supplied with two poison-glands connected with the barbed tail. The secretion is a clear, acid fluid. It induces local inflammation and resembles the poisons of the toad and salamander.

Poisonous Spiders.—All true spiders are supplied with poisonous glands; and besides these organs, some secrete from the entire surface of the body a poisonous substance. The secretion of the glands is a clear, oily, acid fluid, which varies in intensity of effect in different species. Among the best known of the more poisonous spiders may be mentioned the tarantula, the malmignette, and the katipo. The secretion of the malmignette is believed to be the most active of all animal poisons. In the southeastern part of

Russia, camels, sheep, and horses, as well as men, sometimes die from the bite of this spider. The local reaction is slight or wholly unobservable. Death generally follows a long-continued and painful paralysis of the extremities. The local effects of the bite of the tarantula consist of swelling, infiltration, and possibly necrosis. It is believed that the active agent in the poisonous secretions of spiders is a proteid, but we have no positive knowledge on this point.

Spanish Fly.—Cantharidin, the active principle of this beetle, is stored in largest quantity in the sexual organs. The dried beetle contains about $\frac{1}{2}$ per cent. of the poison. There is also present a volatile oil, of characteristic odor; and this, as well as the cantharidin, acts as a local irritant. Cantharides is known to be one of the most active vesicants. The serum that collects in a Spanish-fly blister is characterized by the small number of leukocytes present. It is supposed that cantharidin has a paralyzing effect on the leukocytes. Taken internally, this substance acts as an irritant on the digestive organs and kidney. A glomerulonephritis, with blood and casts in the urine, may be due to internal administration or to the application of a large blister. There may also be desquamation of the epithelium of the bladder.

Bees and Ants.—The poisonous secretions of bees and ants contain formic acid and undecan. The sting of a bee is usually followed only by slight pain and swelling. However, if the sting be left in the skin, supuration may result; this is probably due to infection. When the sting pierces a blood-vessel, death may result from the formation of thrombi. A sting on the tongue or in the pharynx may cause an edema of sufficient extent to lead to death from suffocation. When many bees sting a man, there may be delirium, coma, and death, without thrombi.

BACTERIAL POISONS.

This is not the place to discuss the pathology of the toxins of the specific pathogenic bacteria; such a discussion would properly come under a description of the specific diseases. We will proceed to a very brief statement of the pathologic conditions induced by certain nonspecific toxicogenic bacteria that sometimes occur in articles of food.

Meat Poisoning; Botulismus.—Postmortem examination after sausage poisoning, as a rule, shows no characteristic lesion. Some have stated that putrefaction sets in very tardily; but no reliance can be placed upon this, since Müller found that, out of forty-eight recorded autopsies, it was especially stated in eleven that putrefaction rapidly developed. In some instances hyperemia of the stomach and intestinal canal has been observed, but this is by no means constant. The liver and brain have been reported as congested; but this condition might result from failure of the heart, and would be by no means characteristic of sausage poisoning. Von Faber held autopsies upon four persons killed by eating poisonous sausage. The skin was rough, the abdomen was retracted, the large vessels in the upper part of the stomach were filled with dark blood. The contents of the stomach consisted of a reddish-brown semifluid substance giving off a repugnant acid odor. In one of these cases the omentum was found to be greatly congested. The large intestine was very pale, and the right ventricle of the heart was filled with dark fluid blood.

In cases recently studied at the University of Michigan, a severe follicular enteritis of the small intestine was found. The solitary glands and Peyer's patches were greatly swollen, showing on microscopic examination edema, small-cell infiltration, and necrosis of the central portion. Numerous small hemorrhages, and shallow ulcerated patches of irregular size and distribution, occurred throughout the mucosa. The entire colon showed a very marked diphtheritic colitis, with large irregular ulcers extending to the muscular coat, which in some places showed a marked small-cell infiltration and edema. The blood-vessels throughout were greatly congested and showed a leukocytosis. The kidney presented the picture of an acute parenchymatous nephritis added to that of a chronic nephritis. All of the cells of the convoluted tubules showed extensive cloudy swelling and fatty degeneration, and areas of hemorrhagic and leukocytic infiltration occurred throughout the cortex.

In animals killed by being fed upon poisonous sausage, Ballard found that most of the urinary tubules contained casts, while many of the Malpighian bodies with their surrounding tissue were in a state of disintegration—without, however, any inflammatory cells being present, thus indicating that the disintegration was the direct result of some destructive agency circulating in the vessel. In some cases of poisoning from tinned salmon, Klein found necrosis of the superficial layers of the mucous membrane of the stomach, fatty changes of the liver resembling those of acute poisoning with phosphorus, and also inflammation of the kidneys. Mice fed upon this salmon died, exhibiting lesions similar to those found in man. In some cases of poisoning from veal pie, the same authority found that animals fed upon this food showed no ill effects until the feeding had been continued for three days, after which some of them died; postmortem examination gave evidence of intestinal inflammation and congestion of the kidneys. In still other animals killed by cultures obtained from poisonous meat, Klein found that the liver and kidneys were congested and dark, while the lungs were dark red and almost hepatized. The small intestines were relaxed and filled with mucus.

Gärtner observed desquamation of the epidermis in persons poisoned with meat; even boiled cultures of the germs obtained from this meat were found to be highly poisonous.

Lubarsch reports an interesting case in which the anatomic examination showed pleuritis and pneumonia of the left lower lobe, bilateral bronchitis, atelectasis of the right lung, granular changes in the kidneys, infiltration and engorgement of the liver, slight enlargement of the spleen, uric acid infarction of the kidneys, and icterus. In all animals poisoned with the germ obtained from this case, section showed marked congestion of the intestines, swelling of the follicles, and in some instances slight hemorrhages in the mucous membrane. After intraperitoneal inoculation, serofibrinous or hemorrhagic peritonitis developed. After subcutaneous inoculation in rabbits, there was a serofibrinous pleuritis with compression of the lungs, and in one instance a circumscribed pneumonia. Animals inoculated by Basenau with the poisonous germ obtained from meat showed the following condition: The tissue about the place of inoculation broke down, forming a yellowish-white structureless mass. The surface of the liver was covered with pin-head grayish-white foci of inflammation, giving to the organ a marbled appearance. The spleen showed a similar condition, and both organs were somewhat enlarged.

Animals inoculated with a poisonous germ obtained by Perkins and the writer from some pressed chicken, that had seriously affected a large number of people, showed evidences of abdominal pain within from one to two hours, and several of them were found dead after twelve hours. The abdominal cavity was filled with a clear fluid, the blood-vessels were much congested, and the peritoneum reddened. In some instances a bloody fluid was found in the pleural cavity.

Van Ermengen has isolated a poisonous bacillus from meat, and his observations have been repeatedly confirmed by others.

Poisonous Milk and Cheese.—Up to present writing, the poisons formed in cheese are apparently due to three classes of germs, which vary markedly in their virulence. One class of these germs produces a highly poisonous basic substance, to which the name tyrotoxinon has been given. After experimental poisoning with tyrotoxinon, the mucous membrane of the stomach and intestines is found to be very pale. The most characteristic postmortem condition consists of tightly contracted areas in the intestines. Another class of cheese-germs produces a poison which has not as yet been isolated, and which has a muscarin-like action, but induces no characteristic postmortem lesions. A third class of harmful germs found in cheese belongs to the colon group. The symptoms and postmortem appearances induced by this group vary greatly, as the virulence of the germs themselves is subject to great variation. An animal inoculated with a poisonous germ obtained from this class of cheese may show no anatomic lesions, while, on the other hand, there may be marked hemorrhages in the omentum, the mesentery, and the walls of the intestines.

THE GENERAL PATHOLOGY OF FEVER.

BODILY TEMPERATURE.

THERE is no more wonderful phenomenon in the animal economy, perhaps, than the constancy of the bodily temperature. Notwithstanding great variations constantly taking place in the production of heat and in the loss of heat, the temperature of the body does not vary more than 1° C. in man. In the lower homoiothermal animals the variation is distinctly greater than in man, but even in them the temperature is remarkably uniform. Before considering the abnormality of these functions in fever, let us consider briefly what conditions influence the heat-processes normally and how the normal bodily temperature is maintained.

NORMAL VARIATIONS OF BODILY TEMPERATURE.

The temperature of man varies according to the part of the body at which it is noted. According to Pembrey, the mean daily temperature of the axilla is 36.9° C. (98.45° F.); that of the mouth, 36.87° C. (98.36° F.); that of the rectum, 37.2° C. (98.96° F.). Of course, there is some variation of a fraction of a degree from these figures in either direction in different individuals.

Time of Day.—The temperature of man is subject to slight diurnal variation, rising during the afternoon and early evening until the maximum is reached at from 5 P. M. to 9 P. M. There is a steady gradual fall from this time till early morning, the minimum usually occurring between 2 A. M. and 4 A. M. This variation is usually less than 1° C.; it is generally attributed to muscular activity and taking food during the day, although the writer found the same diurnal rhythm to exist in rabbits deprived of food and exercise.

Muscular exercise may, if it be violent and continued for an hour or longer, cause a transitory rise of temperature of one degree or so for a very short time, but this rapidly disappears after the exercise ceases. The production of heat is increased enormously by muscular work, but it is usually compensated for by increased loss of heat during and soon after the exercise.

Food.—There may be a slight rise of temperature after a hearty meal; here again increase of the heat produced is rapidly balanced by increase in the heat-loss. Abstinence from food causes the bodily temperature to fall slightly.

External temperature causes slight variation in the bodily temperature. The temperature of man in the tropics is not over 0.5° C. above that observed in temperate climates, while the temperature of men in Arctic regions shows no greater variation in the other direction; further, the temperature of animals in Arctic regions is the same as that of animals of the

same classes living in temperate climates. The external temperature, then, may vary from $+50^{\circ}\text{C.}$ to -50°C. , while the bodily temperature will not change more than 1°C.

As to the extremes of external heat or cold that can be borne with impunity, much depends upon the degree of moisture present in the air. James found that 80°C. caused little inconvenience as long as the air was dry, while a vapor bath at 44.5°C. could only be tolerated a short time. A moist air at 45°C. will soon cause a rise of bodily temperature.

Water is a much better conductor of heat than air, and, further, prevents evaporation. A cold bath can be resisted by a normal man for a considerable time without much reduction of temperature, although the loss and production of heat must be enormously increased. Thus, remaining in a bath at 25°C. for three hours caused a fall of temperature of but 0.6°C. ; a bath at 15°C. for the same length of time caused a fall of only 1°C.

On the other hand, a warm bath will raise the temperature of the body after a few minutes, although it may not be nearly so much above the temperature of the individual as the cold baths just mentioned are below it. Remaining in a bath at 45°C. for ten to twelve minutes will cause a rise of bodily temperature of 2.5°C. , which rapidly disappears after leaving the bath.

Age seems to have very little influence on the degree of temperature. The surface-temperature of the aged may be lowered from imperfect circulatory conditions, but the rectal temperature is unchanged. The temperature of infants may be a trifle higher than that of adults, but this is insignificant. The *instability* of the temperature of children, however, is very pronounced and characteristic. Slight causes which would not affect the temperature in adults will cause a tremendous elevation of temperature in children.

CONDITIONS INFLUENCING HEAT-PRODUCTION OR THERMOGENESIS.

Muscular Exercise.—It is estimated that the production of heat is from one to three times greater during muscular exercise than during rest.

Food.—The production of heat is from 30 to 40 per cent. greater when food is taken than when it is withheld; there is considerable increase after each meal. The character of the food also influences the amount of heat produced, fats being more than twice as valuable in this respect as either proteids or carbohydrates.

Conditions Affecting Heat-Dissipation Primarily.—**Size.**—Generally, among animals of approximately the same size, the production of heat depends upon the body-weight. However, when there is a great difference in size, the smaller ones produce relatively much more heat than the large ones. This is because the external surface is much greater as compared with the bulk, and the loss of heat is in proportion to the extent of surface. The production must balance the loss, to maintain the bodily temperature.

External Temperature.—A low external temperature increases the production of heat, because the loss of heat from the body is greater notwithstanding the efforts of Nature to limit the latter. On the other hand, a high external temperature may lessen the heat-production to a certain extent; but this diminution cannot be as great as the increase in a cool environment.

The muscles constitute from 42 to 45 per cent. of the body-weight; and as the greater part of the chemical changes of the body occurs in them, they form the chief seat of the production of heat in the body. As the heat produced in other tissues is

tolerably constant, it is highly probable that variations in thermogenesis are caused chiefly by variations in the heat produced by muscles. According to Stewart, removal of the nervous control of voluntary muscles by poisoning with curare reduces their metabolism to one-fifth of the normal and reduces the total heat-production of the body 35 per cent. He divides the remaining 65 per cent. as follows: Heart, 15; skeletal muscle, 10; all other tissues, 40. Of course, when muscles are contracting, heat is necessarily produced in great quantities, as four-fifths of the energy expended reappears as heat. But even when there is no mechanic work performed at all, the muscles produce nearly as much heat as all the other tissues of the body put together. All the chemical potential energy may be converted into heat, or a part of it may appear as work.

The heat-production and heat-dissipation can only be measured for short periods of time with any accuracy by either air or water calorimeters. Unfortunately calorimeters large enough to admit men are not very accurate, although small ones for animals may be fairly constant. However, the measurement of heat-loss and heat-production is not as simple or easy a matter as it might appear. Measurements of heat lost to water by placing a man in a bath are worthless, as at most only the heat from the skin could be recovered; while the water, being so much more conductive of heat than air, places the individual under abnormal conditions.

The respiratory quotient ($\frac{\text{CO}_2}{\text{O}_2}$) may be taken as an index of combustion in the tissues, and thus indirectly of heat-production, if the diet be unaltered. This is not so valuable when used for short periods of time, as oxygen may be stored in the tissues for some time, and altered conditions of the blood may influence the CO_2 given off.

Methods of measuring the heat produced, by calculations from the heat values of the foodstuffs absorbed and excretions given off, are of little use in the study of fever. Both the production and the loss of heat are fluctuating, and at best no idea of the relation between the two could be gained. In most cases of fever, disintegration of the permanent tissues is going on to a great extent.

CONDITIONS AFFECTING HEAT-LOSS OR THERMOLYSIS.

From 75 to 80 per cent. of the heat lost from the body is given off by the skin, chiefly by radiation and conduction, and to a much less extent, under ordinary conditions, by evaporation. The lungs give off from 15 to 18 per cent. of the total heat-loss, chiefly by evaporation and to a much less extent by warming the air.

Heat-dissipation or thermolysis will, therefore, depend upon the following conditions: The covering of the body, the external temperature, the condition of the blood-vessels on the surface and the rapidity of the circulation, the activity of the sweat-glands, the deposit of subcutaneous fat, the relative humidity of the air, and the volume of air moved in and out of the lungs. Of course, anything primarily affecting heat-production—*e. g.*, food, exercise, etc.—will, in the normal body, affect heat-loss secondarily. Small animals lose much more heat per kilo. of body-weight than large ones, their surface being proportionately much greater.

There is no daily variation in the heat-production and heat-dissipation corresponding to the diurnal rhythm of bodily temperature.

THE MAINTENANCE OF A CONSTANT TEMPERATURE.

However great the variations, both of heat-production and of heat-loss, from hour to hour, caused by the many conditions of daily life, the bodily temperature is but little affected by any of them. The temperature does not depend upon either the one or the other alone, but upon the *relation between the two*. The balance can only be maintained by some regulating mechanism which can control both processes, so that when one is affected primarily the other may be adapted accordingly. Thus, when the produc-

tion of heat is increased from exercise, the dissipation is changed correspondingly by accelerated respiration and circulation, dilated peripheral vessels, and active sweat-glands. On the other hand, when heat-loss is primarily increased, as by exposure to low external temperature, the superficial vessels constrict to keep the blood from the surface. Nature makes every effort to reduce the thermolysis to a minimum; but if it be still increased, the production of heat increases to keep pace with it.

Ordinarily the regulation of bodily temperature is effected chiefly through changes in thermolysis, and the range of variation in loss of heat from the body is a wide one. The means of increasing or decreasing heat-dissipation are numerous, provided surrounding conditions are favorable for such changes. When, however, the temperature of the atmosphere is near that of the body and contains a high percentage of moisture, the limit of regulation is soon reached, because the dissipation cannot be increased as usual.

Although the production of heat may be increased in a *low* external temperature, it cannot be decreased in a *high* external temperature as much as is often supposed.

Altogether, extremes of cold can be borne with less discomfort than extremes of heat; it is a remarkable fact that the bodily temperature may be reduced as much as 12° C. (21.6° F.) and recovery occur (Nicolaysen), while an increase of half that amount is extremely dangerous and usually fatal.

Reasons for Believing the Nervous System is the Controlling Factor.—From the great and constant variations, both of thermogenesis and of thermolysis, it is hard to conceive how the regulation of bodily temperature or thermotaxis can be brought about in any other way than through the influence of the nervous system. Although the various means of thermolysis have long been recognized as governed by nerve-centers, the control of heat-production or thermogenesis, and of heat-regulation or thermotaxis, by the nervous system, has been much more difficult to prove and has only been established in recent times. While there can be no doubt as to the main facts, the exact functions of some so-called "heat-centers" have not been made clear.

Bernard's observation on the rise of temperature in the rabbit's ear after section of the cervical sympathetic was the starting-point of our knowledge of the influence of the nervous system on the heat-processes. His view that the rise of temperature was independent of the vascular change and due to the removal of an inhibitory influence over the heat-production in the tissues has not been confirmed by others. Similarly the alterations of temperature resulting from stimulating sensory nerves or the spinal cord, as recorded by Heidenhain, Riegel, and Tangel, were doubtless brought about by changes in the circulation.

It is unnecessary to assume that there must be specific thermogenetic nerve-fibers for such a nervous control. It is sufficient to prove that the chemical changes taking place in the tissues are regulated by the nervous system, and that such changes can be varied independently of the ordinary performance of work by the various tissues. The most valuable experiments in this direction are those showing great alterations in metabolism from removal of the nerve-control of muscles by poisoning with curare. Curare produces paralysis of the motor nerve-plates, vasodilatation, and causes the bodily temperature to fall, if the temperature of the air is lower—or to rise, if the temperature of the environment is higher—than that of the

body. Even if the normal bodily temperature be artificially maintained, the gaseous interchange is greatly altered—the intake of oxygen falling about 35.2 per cent. and the output of CO_2 falling 37.4 per cent. When the temperature of the animal is raised artificially, the respiratory exchange is increased; when lowered, it falls. These changes are not due to a deficient supply of oxygen, as it was abundantly furnished by artificial respiration. They are not due to any direct action on the sarcous substance, as muscles artificially perfused with blood containing curare show the same oxidation as when the blood does not contain the poison. The only explanation is the separation of the muscles from the nerve-centers governing them; and as the muscles produce most of the heat of the body, thermogenesis is very materially affected. The mere diminution of heat-production and of these chemical changes is no more significant than is the fact that heat-regulation or thermotaxis is lost, so that a homoiothermal or so-called warm-blooded animal becomes a poikilothermal or so-called cold-blooded animal under the influence of curare. The animal can no longer adapt its heat-processes to the environment, and the bodily temperature varies with external changes. This is not due merely to the vasodilatation, but chiefly to the paralysis of the voluntary muscles.

Section of the spinal cord high up in the cervical region removes the power of thermotaxis. The bodily temperature rises with high external temperature or excessive covering of the body, and falls with low external temperature. The production of heat is lessened by the muscular paralysis, while the loss is increased by the vasodilatation. Thermolysis may also be interfered with by disturbances of respiration and sweating.

Generally the bodily temperature falls after injury of the spinal cord. A few cases of hyperpyrexia after injuries of the cord have been recorded; it is difficult to explain these.

Efforts to localize "heat-centers" in the brain have led to conflicting and confusing conclusions. The claims of different investigators are so at variance that no definite function can be attributed to these various centers. The most we can say is that injury of certain parts of the brain produces a rise of temperature with consequent changes of metabolism, the elevation of temperature lasting a variable time.

The parts, injury to which has these effects, are as follows: 1. Cortex: (a) The neighborhood of the cruciate fissure and just back of it (dogs and cats); (b) the junction of the supra-Sylvian with the post-Sylvian fissure (cats). 2. Basal ganglia: (a) Pons; (b) corpus striatum (dogs, cats, and rabbits); (c) optic thalamus (rabbits only).

Most of these experiments have been performed upon rabbits. The temperature of these animals is unstable and easily influenced by slight disturbances. Injury to some of the areas claimed to be heat-centers in rabbits does not cause rise of temperature when occurring in corresponding areas in dogs. On the other hand, the operative procedure in some of the experiments upon dogs is enough to produce such a condition of shock as to vitiate any results.

Again, different conclusions have been reached concerning the same area. Thus, the first experiments showed that section between the pons and medulla caused rise of temperature and increased heat-production and heat-dissipation. The conclusion was that there was an inhibitory center in the pons or above it which normally controlled a hypothetic augmentor center in the medulla (Tscheschichin, Wood). Subsequent observers found that such sections produce a fall of temperature as often as they cause a rise, and further that puncture with a probe or electric stimulation of the pons will cause quite as great a rise; and they reach the conclusion that the center in the pons is an augmentor center (Bruck-Günther, Schreiber).

Another observer (Ott) produced rise of temperature by puncturing the pons, but claimed that he had injured fibers from higher centers and not nerve-cells. The same observer, however, has attributed similar results after injuries to the basal ganglia to injuries of nerve-cells.

Areas in the cortex are claimed to be thermo-inhibitory because a rise of temperature ensues when they are injured, while other areas in the basal ganglia are assumed to be augmentor, although similar injuries with a probe cause a rise of temperature.

One observer considers the cortical centers to be thermotactic, while another considers them to be thermogenetic, because the fever is established with an increase of heat-production. Pyrogenic poisons are generally supposed to act upon thermotaxis.

Some experiments by Ott indicate that injury of the corpus striatum interferes with the rapid respiration (polypnea) produced by exposure of furred animals to hot air. He calls this a thermopolypneic center; he also claims vasomotor changes from injury of the optic thalamus. If these are correct, these parts are concerned in thermolysis. In another communication Ott claims these centers are thermo-inhibitory (*i. e.*, thermogenetic); at another time he considered the centers in the basal ganglia as thermotactic. Calorimetric experiments do not indicate that thermolysis or heat-dissipation is primarily disturbed by puncture of these centers. It is not clear why destruction should act in the same way as electric irritation by the Faradic current, as Aronsohn and Sachs obtained the same result by either method; or why one center in the cortex should be considered thermotactic, while another at the base, which when destroyed in the same way causes fever to be brought about in the same manner, should be considered thermogenetic. Some of the experiments are not conclusive, while certain deductions drawn from them are not justified.

FEVER.

Definition; Stages.—The term fever is sometimes used loosely to signify a mere rise of temperature above normal. There are, however, conditions of elevated temperature which are not febrile—*e. g.*, the transitory rise of temperature after a hot bath or from violent exercise, in either of which the condition is within physiologic limits. So, too, the mere rise of temperature in children caused by crying or teething, or the sharp rise of temperature sometimes seen in hysteria and occasionally from passing a catheter without infection ("urethral fever"), probably may be regarded as due to a temporary disturbance of the normal regulation of the heat-phenomena of the body, without the usual conditions occurring in fever.

The pathologic state, *fever*, is indicated by a group of symptoms as follows: (*a*) Rise of temperature, (*b*) altered metabolism, (*c*) increased activity of circulation and respiration, (*d*) functional changes, (*e*) structural alterations in various tissues of the body. Of these conditions the first two are the most important, and the functional and anatomic changes may result from them. Generally the poisons causing the rise of temperature also produce all the other conditions. Sometimes these conditions, which are often regarded as secondary, are out of proportion to the elevation of temperature, as is quite often the case in diphtheria.

On the other hand, the mere pyrexia or elevation of temperature alone may be primary, and all the other conditions secondary, as is clearly the case in thermic fever and probably in that produced by injury of nerve-centers.

While the rise of temperature (pyrexia) is the most prominent and most constant condition, it is not an absolutely essential symptom of fever. Sometimes in septicemia, and very rarely in typhoid fever, the other conditions of fever may be present without elevation of temperature. Indeed, in uremia, the same poisons which at times cause marked pyrexia may in other cases cause a fall of temperature. Considerable confusion has arisen from apply-

ing different meanings to the word "fever." Perhaps it would be better to use "fever" to include the entire group of phenomena, and "pyrexia" for the most conspicuous one—the rise of temperature.

We generally estimate the severity of the fever by the degree of pyrexia, although, as has just been said, this is not always an index. Thus, when the temperature is not over 37.7° C. (100° F.), it is spoken of as "slight fever"; between 37.7° and 39.4° C. (100° – 103° F.), it is considered as "moderate fever"; between 39.4° and 40.5° C. (103° – 105° F.), it is "high fever"; while over 40.5° C. (105° F.), it is regarded as "hyperpyrexia."

The course of most fevers can be divided into three stages, as follows: 1. The *initial* or "*cold*" stage, when the temperature is rising. 2. The *fastigium* or "*hot stage*," when the temperature is at a fairly constant level above the normal. 3. The *terminal stage*, the *period of decline or defervescence*, when the temperature is falling.

The **initial stage** usually starts with chilliness, and often with a distinct chill if the onset be sudden. The patient feels cold and the surface-temperature may be subnormal, although the internal temperature has already risen considerably above the normal. The elevation of temperature precedes the chill, although it is still rising during the cold stage. The rigor or shivering may increase the heat-production from muscular contraction. The skin is generally pale, but is sometimes cyanotic. Although the heat-loss from the surface is diminished in this condition, it is not the primary cause of the rise of temperature. Studies of malarial fever with the plethysmograph show that the elevation of temperature antedates the vasoconstriction of the surface-vessels.

The **second stage** or **fastigium** varies from a few hours to as many weeks in duration. Usually when the subjective sense of chilliness passes off, the temperature has attained its height. The cutaneous vessels dilate and the skin is flushed. It feels hot and dry to the touch, but the actual amount of sweat from the surface may be increased even in this condition. The internal temperature is tolerably constant, but may fluctuate considerably. The diurnal variation, with the maximum in the evening and the minimum in the morning, is usually present, but is not as regular as that seen normally. The surface-temperature is subject to wide variations during this stage.

The **terminal stage** may occupy several days, the temperature gradually falling a little lower on each successive day (termination by "lysis"). It may occupy but a few hours, when the fever is said to end by "crisis." In this latter condition there is profuse perspiration, or sometimes diuresis and acceleration of the respiration. The great increase in the heat-loss indicates an effort to restore the bodily temperature to normal.

DISTURBANCE OF THE HEAT-PROCESSES IN FEVER.

As the elevated temperature is the most conspicuous and most constant condition of fever, the question is naturally suggested: How is this rise of temperature produced?

Theoretically the condition could be effected in a number of ways or combinations of disturbances of thermogenesis and of thermolysis.

Clinical observation alone would lead us to suppose that there is tremendous diminution of heat-loss during the initial stage, and a corresponding

increase during the terminal stage. This would indicate that fever is due to heat-retention; but this theory (Traube's theory) is no longer held, for it has been found that usually the increase of production is greater than the decrease of heat-loss during the initial stage. Moreover, the rise of temperature precedes the cold stage. During the fastigium or hot stage, the hot and dry skin alone would lead one to suppose that loss of heat by evaporation is greatly decreased, although the loss by radiation and conduction is increased. We still need more extensive and accurate measurements of the former means of heat-loss, but the observations recorded indicate that the loss of water from the skin may be increased, although the skin feels dry.

Clinical observations as to the condition of the skin do not give accurate information as to the total heat-loss, the heat-production, or the relation between the two. These can only be determined by calorimetric observations. Unfortunately an apparatus large enough to contain a man has not been constructed so as to give constant and accurate results. Efforts to

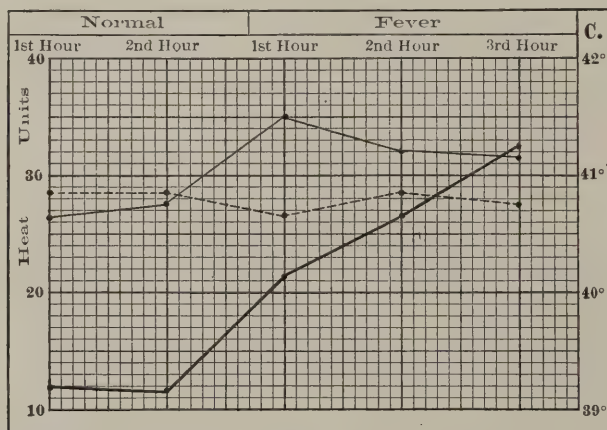


FIG. 136.—Composite curve showing how pyrexia is produced. Heat-units on the left; degrees of temperature (Centigrade) on the right. Continuous line represents heat-production; dotted line represents heat-dissipation. Heavy line below represents the temperature.

measure the heat-loss by placing a febrile patient in a bath, as was done by Liebermeister, or by placing one limb in a calorimeter, a method followed by Leyden and by Rosenthal, are open to much criticism.

The most reliable information as to the heat-processes in fever is derived from calorimetric observations on animals made febrile experimentally. But even the smaller instruments are not as accurate as they might be. A careful examination of the changes of temperature, compared with the changes in the production and loss of heat, will show many discordant results; but we can accept the gross changes, as they are quite constant.

Experimental evidence indicates that there is an increase in heat-production in pyrexia, over the heat produced by the normal animal in the fasting state; but less is produced than in a condition of health on a full diet. The total average increase is not over 25 per cent. of the normal, under similar conditions of diet. The increase, however, is not as great as the hot, dry skin during the hot stage of fever would lead one to infer.

Indeed, the increase is greater in the early stage during the *establishment* of the fever than during its *continuance*, as can be seen by examining the curve in Fig. 136. This is a composite curve made from twenty calorimetric experiments on dogs, the fever having been produced after the second hour by the intravenous injection of putrid blood (5 drops) every hour.

Although the heat-loss is less during the establishment of fever than during its height, it is usually greater than the normal. *In experimental fever at least, the pyrexia appears chiefly to be due to increased production rather than to diminished loss of heat.* Exceptionally it happens that fever is established by a great diminution of thermolysis without any increase of thermogenesis.¹ Possibly, as W. Hale White pointed out in his Croonian Lectures,² we are too prone to generalize and apply these results to all fevers in man. White contends that pyrexia in man is established in some cases by increased thermogenesis, in others by diminished thermolysis. While this may be true, his method of determining heat-loss and heat-production from the internal temperature, the surface-temperature, and evaporation of sweat, is not beyond criticism. Of course, if both conditions are present, they conjoin to produce a still greater rise of temperature.

During the stage of defervescence, the production of heat falls and its dissipation increases, the latter being out of proportion to the former when the fall is rapid. This change can be seen by the curve in Fig. 137. This is a composite curve representing five experiments of two days each. The curve on the left shows how fever was established the first day; that on the right the normal the first hour, the production of fever by giving the same amount of putrid blood as the day before (5 drops) every hour after the first hour, and the reduction of temperature beginning the third hour, one hour after its administration by the stomach. The average dose of antipyrin was 0.93 gm. per kilo. of body-weight.

In fever, as in health, there is absolutely no relation between the amount of heat produced and the bodily temperature. Although the heat-production is increased on the average, it is no greater than in health on a full diet and probably not as great as in many conditions of health, *e. g.*, muscular exercise, exposure to cold, consumption of large amounts of food. It is therefore evident that *fever does not result from the mere increase of heat-production alone, but from a disturbance of heat-regulation or thermotaxis.* The athlete, in playing a game of football or rowing in a boat-race, probably produces more heat than is produced in the establishment of the most severe fever; but the temperature does not rise, because thermolysis keeps pace with increased thermogenesis. It is this *relation between the two* that is disturbed in fever, and *not the absolute quantity of heat produced.*

This view is rendered the more probable from the way in which most antipyretics act upon *both* the production and the dissipation of heat, to restore the normal temperature (see Fig. 137). Antipyretics do not affect the temperature of the normal animal materially, and neither do they affect heat-production or heat-dissipation, as can be seen in Fig. 138.

Agents which produce pyrexia probably do so by acting upon nerve-centers which regulate the heat-processes of the body (thermotactic centers).

The theory of Liebermeister, that in fever there is still thermotaxis, but

¹ Ott, *Journ. Nerv. and Mental Diseases*, 1889; Wood, Reichert, and Hare, *Therapeut. Gaz.*, 1896.

² *Brit. Med. Journ.*, 1897, vol. ii., p. 1653.

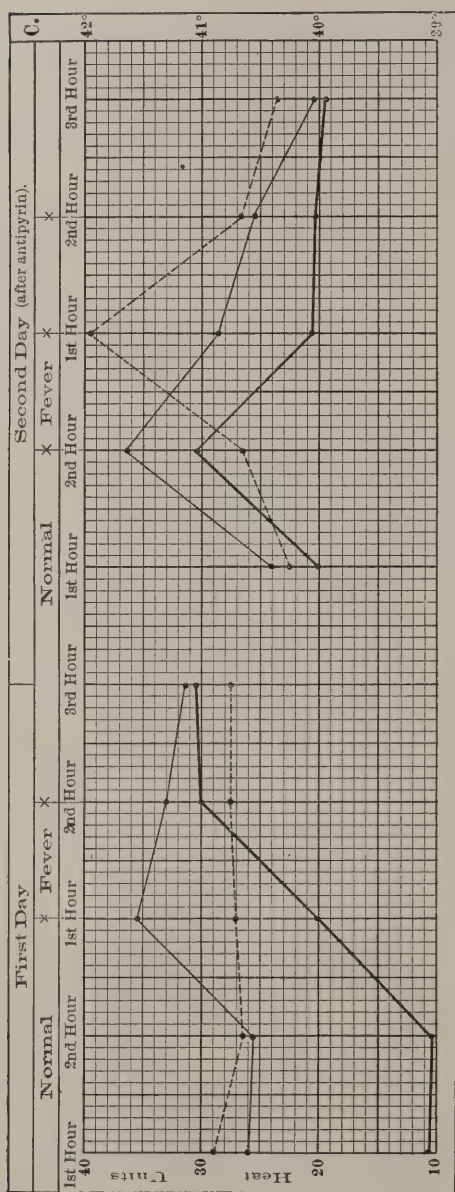


FIG. 137.—Composite curve from five experiments. Continuous line — heat-production; dotted line = heat-dissipation; heavy line = temperature. Fever produced after second hour on first day; after first hour on second day. 0.99 gm. antipyrin by the stomach at second hour, second day. * marks the injection of 5 drops of putrid blood.

simply set for a higher level, just as we would set the thermostat of an incubator in the laboratory for a temperature several degrees above that ordinarily used, is no longer tenable. According to this theory, to quote

MacAllister, man's thermal mechanism in fever would simply correspond to that of a bird under normal conditions.

We have already seen that normal thermotaxis is remarkable for its *stability*. The temperature in fever is characterized by its *instability*. The surface-temperature is constantly changing within wide limits and independently of the rectal temperature. The internal temperature is not subject to as great fluctuations as that of the surface, but varies vastly more than in the normal state and is very unstable, being easily changed to a great extent by agents which scarcely affect the normal temperature. Cold baths and antipyretic drugs cause a tremendous fall of temperature in fever, but not in the normal animal.

Baths seem to do far more good in restoring heat-regulation in fever than in the mere physical abstraction of heat. They probably act on the nerve-centers reflexly through the skin to re-establish thermotaxis.

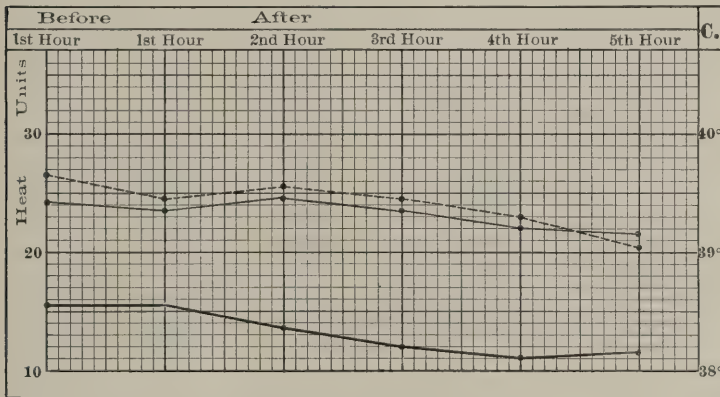


FIG. 138.—Composite curve of eight experiments, showing effect of antipyrin on normal animals. Continuous line = heat-production; dotted line = heat-dissipation; heavy line = temperature. Average dose hypodermatically = 0.19 gm. per kilo.

Welch¹ has also shown in his Cartwright Lectures that rabbits made febrile by puncture of the corpus striatum are unable to withstand exposure to an atmosphere of either high or low temperature without showing far greater variations of the bodily temperature than a normal animal shows.

All these facts point to the conclusion that in fever there is a lack of thermotaxis or heat-regulation.

CAUSES OF DISTURBANCES OF THERMOTAXIS IN FEVER.

Injury of Nerve-centers.—We have already considered the parts of the brain, injury to which, in the lower animals, produces fever. Clinical reports of lesions of these parts in man indicate that they control the heat-processes, and, when disturbed, fever is caused—just how, we cannot say. The inability of animals to adapt themselves to different external temperatures, after injury of some of these centers, would indicate that they are thermotactic. On the other hand, the fever lasts but a short time after such injury, and it is remarkable how constantly the pyrexia is established by

¹ *Med. News*, April and May, 1888.

increased thermogenesis alone. Perhaps the highest temperatures in man are those caused by lesions of the pons Varolii.

Exposure to high external temperature, particularly if the air contains a high percentage of moisture, in a short time causes the bodily temperature to rise to a height seldom seen in specific infections. The condition seems to result from a loss of control of the heat-processes by the nervous centers in consequence of overstimulation or overactivity of the mechanism in the effort to regulate the temperature under such unfavorable circumstances.

Although the rise of temperature is apparently the primary disturbance in this condition, increased oxidation and the usual alterations of metabolism, functions, and structure follow if the pyrexia continues any length of time.

The toxicity of the blood in thermic fever probably results from the disturbance of metabolism brought about by the pyrexia.

Poisons.—Some drugs act as pyretics, as atropin, strychnin, cocain, and caffein; also numerous substances, such as β -tetrahydronaphthylamin, commercial peptone, papoid, pepsin, etc. The pyrogenic agent of the latter seems to be a peptone.

By all means the most frequent causes of fever in man are the products of bacteria (toxins), which probably act in some way upon nerve-centers to produce pyrexia.

By some it is supposed that these poisons act directly upon the tissues to produce fever (the so-called hemic theory of fever). Such action could only produce pyrexia by increasing the heat-production, and we have already seen that fever is due not merely to an increase of production, but to a disturbed relation between thermogenesis and thermolysis.

Pyretic drugs, as cocain and caffein, fail to produce fever in the usual way in animals poisoned by curare (Reichert). Curare merely removes the nerve-control of muscles; it does not act on the tissue-substance or interfere with its metabolism in any way.

CHANGES IN FEVER.

Metabolic Changes.—There is increased oxidation in fever. The amounts of oxygen absorbed and CO_2 given off are both increased, although the relation between them ($\frac{\text{CO}_2}{\text{O}_2}$, or respiratory quotient) is practically unaltered. This indicates that, although the amount of combustion is increased, the substances oxidized are probably the same as in health under similar conditions of diet.

The amount of urea eliminated in fever is greatly in excess of the amount given off by a healthy person on the same diet; this indicates an increased destruction of proteids in the body. As the amount of nitrogen absorbed from the alimentary canal is less than the output in the urea, some of it comes from the permanent tissues of the body. This fact is also made known by the great emaciation seen in febrile patients. The fats likewise disappear from the tissues, the resulting metabolites being CO_2 and H_2O .

Uric acid is also increased, but is somewhat variable in amount. This results from the metabolism of nucleoproteids. The N of proteids is probably eliminated entirely as urea and has nothing to do with uric acid. The metabolic changes producing these two classes of materials are distinct, and each one is influenced by different conditions. Although there is generally a

fairly uniform proportion between the amounts of uric acid and urea in the urine, this is by no means constant. The amount of uric acid probably depends upon the degree of leukocytosis (or rather of leukocytolysis) more than upon any other factor. Even when there is no leukocytosis, there is some increase of uric acid, probably coming from the nuclei of the fixed tissues.

The increased oxidation is generally regarded as a part of the febrile process, and not the result of the high temperature. There seems to be no relation between the elevation of temperature and the amount of oxidation. It has been found in intermittent and in septic fevers that oxidation is increased before the rise of temperature begins, and rapidly reaches its maximum long before the temperature attains its height.

On the other hand, in thermic fever (Welch) and in purely nervous fever produced by cerebral puncture (Ott), there is increased oxidation in rabbits, as is evidenced by wasting of the tissues, although the animals eat greedily. The loss in weight is not due entirely to the loss of water. As the temperature is primarily affected in these latter conditions, we may conclude that the pyrexia may in part cause the increased metabolism, but is not the sole cause of it.

Functional Changes.—Circulation.—The pulse-rate is increased in fever; the increase being, on the average, 8 pulsations for each degree Centigrade or 4.5 for each degree Fahrenheit. While this acceleration, at least in the beginning, is brought about through the nerve-centers controlling the activity of the heart, there is also no doubt of the direct action of warmed blood upon the heart, as has been repeatedly demonstrated by perfusing the isolated mammalian heart. Although the systole is somewhat shortened, the increase in frequency is chiefly at the expense of the diastole or period of rest. When fever continues a long time, as typhoid fever, this may have considerable significance.

The blood-pressure is variable; although it may be increased early, it is nearly always diminished late in fever. The feeble, soft pulse in advanced stages probably indicates a combined condition of weak heart and lessened arterial tension. Welch found that blood-pressure in rabbits kept in a state of thermic fever for two weeks was normal, although there was moderate fatty degeneration of the myocardium. It is quite probable that the peripheral vessels are altered in fever, and this condition contributes in large part to the lessened pressure. Probably there are changes both in the cardiac and vasomotor nerve-centers, as well as in the organs controlled by them.

The dicrotic pulse which occurs late in prolonged fevers indicates great alteration of vasomotor tone. That there are also changes in the blood-vessels before any decrease of pressure occurs is rendered probable from the way in which the vessels in the rabbit's ear or the cutaneous vessels of man react to stimulation which normally produces vasomotor changes. Changes in the blood-vessels seem to be due more to the poisons causing the fever than to the pyrexia alone.

Respiration is generally accelerated in normal proportion to the pulse. Although it may be shallow, the volume of air respired is increased. The frequency is not always in proportion to the temperature. Even in pneumonia, where the local conditions would be expected to determine the rate, the chief cause appears to be the toxemia. This is seen in the abrupt fall in the respiratory rate, with the crisis, before consolidation has disappeared.

Although warmed blood can produce acceleration of the respiration by acting directly on the respiratory centers, the pyrogenic agent probably acts in the same way.

Exposing a furred animal to hot air increases the respiratory rate enormously, as this is the only way these animals have of regulating their temperature. This condition is called "heat-dyspnea" by some, and "thermopolypnea" by others.

Secretions.—*Digestive Secretions.*—The saliva is diminished in amount, and the glands cannot be excited to increased activity reflexly as in health.

The gastric juice is decreased in amount, and there is a great reduction in HCl. Pepsin does not appear to be affected.

The bile is said to be diminished. These alterations of the digestive juices would account for the anorexia and enfeebled powers of digestion which occur in fevered patients. Absorption is also greatly delayed, and peristalsis is retarded.

Sweat is decreased in the early stage, and increased in the terminal stage.

The hot, dry skin is no indication of the amount of sweat given off. W. Hale White found that it sometimes decreased in typhoid fever; but in other diseases (pneumonia and erysipelas), he found that it increased, even when the skin felt dry.

Renal Secretion.—The urine is increased in the cold stage of fever, from the internal congestion and increased blood-supply resulting from the peripheral vasoconstriction. During the hot stage the urine is decreased, because more water is lost through the skin and lungs than is normal. In the terminal stage the urine may become scanty, from the great increase in the loss of water by the skin.

Albuminuria seems to be due to changes in the kidney structure or function, and not to changes in the blood alone. It is not present in all fevers. When it occurs, it does not appear early when the temperature is at its height, but late, when the structural changes are most pronounced. It occurs most frequently in diseases causing pronounced structural alterations in the kidney, *e. g.*, diphtheria, yellow fever, etc.

Changes of the inorganic ingredients, *e. g.*, the increased elimination of phosphates and of potassium salts, the diminution of sodium salts and of chlorids, all result from altered metabolism in the tissues.

Nervous Symptoms.—Cerebral activity is generally dulled, but may be increased but perverted, *e. g.*, delirium, hallucinations. Whether this is due to pyrexia or to the material causing pyrexia, it is impossible to say at present.

Late in the course of prolonged fevers, incontinence of urine and of feces may occur from disturbance of the function in the centers of the spinal cord. Just what structural basis there is for such change of function cannot be stated, but such changes occur in the nerve-cells.

Blood.—All the changes in the blood are variable. The red corpuscles may be normal, increased, or decreased. The differences of distribution of the blood from vascular changes make blood-counts less accurate than in health. Sometimes there appears to be a real destruction of corpuscles. At other times, the seeming increase of corpuscles is only relative, due to increased loss of water from the body or to disturbed circulation.

In most fevers, there is more or less leukocytosis; and even when it does not occur, there is a change in the kind of leukocytes. The writer

found that pyrexia alone, produced by placing animals in a hot box, does not produce leukocytosis. The poison causing the fever is probably the cause of the leukocytosis.

The alkalinity of the blood has been found by some to be increased, and by others to be decreased. These deviations from the normal appear to result either from the direct changes of the pyrogenic agent or from the changes in metabolism. They do not occur in the pyrexia of nervous origin or in thermic fever; and further, the changes in alkalinity do not coincide with the pyrexia. It has been suggested that increase of alkalinity is a favorable sign, showing increased resistance on the part of the animal economy to the infection, while decreased alkalinity indicates the opposite condition.

Structural Changes.—Widespread degenerative changes are commonly found in the tissues after death from febrile diseases. This may be (*a*) parenchymatous degeneration or cloudy swelling, or (*b*) true fatty changes. The former is commonly regarded as a transitional stage of the latter; and the fact that cloudy swelling occurs in mild or rapidly fatal infections, while fatty degeneration only appears after a very severe or prolonged febrile process, lends plausibility to this view.

The tissues showing these changes are the liver, kidney, heart, and voluntary muscles, especially those continuously active in respiration, as the diaphragm.

Whether these degenerations occur as a result of the infection or of the pyrexial process has been the subject of considerable discussion. That the toxemia alone can produce profound changes is seen from the marked structural alterations found after acute infections where there has been little or no pyrexia, as often occurs in diphtheria, sometimes in septicemia, and occasionally in typhoid fever. This degeneration is not the same in all infections, but appears to depend chiefly on the kind and severity of the infection and not on the vigor of the pyrexial process.

On the other hand, pyrexia without any toxemia, produced by keeping rabbits in a hot box with an average rectal temperature of 41.1°C . (106°F .), will produce cloudy swelling and moderate fatty degeneration, if the pyrexia be maintained for at least a week (Welch). This is not constant, however, as Naunyn failed to find it after keeping rabbits in a hot box for two weeks. Welch also found that, the higher and less fluctuating the bodily temperature, the more certain is the degeneration to occur.

It would therefore appear that both factors contribute to the structural changes.

Just how closely these structural alterations are associated with disturbances of function, or to what degree they form a source of danger, cannot be positively stated. Clinicians may overestimate this relation, and pathologists may possibly underestimate it, especially in regard to the heart. In his experiments on rabbits, Welch found that, although they had been confined in a hot box for ten days or two weeks, until the heart showed well-marked fatty degeneration, the normal blood-pressure was maintained and the heart responded to stimulation of the vagus in the usual way. In other words, after pyrexia without toxemia, the structural changes did not prevent the heart from acting in a perfectly normal way, to all appearances.

The weak pulse and feeble first heart-sound observed clinically after severe infections, as well as an occasional sudden death from true heart-

failure, indicate that the changes after toxemia are usually much more severe and the interference with function more serious.

Since the method of staining the neurones of the nervous system by silver impregnation has been used so extensively, profound changes of these cells have been found in at least two infections—tetanus and diphtheria. These consist in a loss of the gemmulæ, great varicosity of the dendrites, and shrinkage of these processes of the cell. More extended observations are needed in other infections and in nontoxemic pyrexia. The meaning of these changes of structure in the neurones is still a matter of controversy, but it is highly improbable that such striking changes as occur in the above-mentioned infections are artefacts or normal variations, although some very slight changes attributed to the influence of some drugs may be such.

THE SIGNIFICANCE OF FEVER.

The real significance of fever has been a matter of much speculation and difference of opinion. Until recent years the opinion has prevailed that the chief source of danger and the main point to be combated by treatment is the elevation of temperature. It is true that high fever which is uncontrollable and does not respond to the usual methods of reducing temperature is of grave significance, not merely from the pyrexia itself, but because it is an indication of the severity of the disease.

Of late years, however, opinion has changed greatly; and the view that fever, or at least a moderate degree of fever, is beneficial rather than harmful, and is Nature's way of defending the organism against the infection, is being more generally accepted. While there may be danger of this idea being carried too far in the treatment of fevers, there can be no doubt that many infections, such as typhoid fever, pneumonia, and sepsis, seem to do better and the prognosis is more favorable when the animal economy responds with a positive but controllable pyrexial process than when there is very little febrile reaction. Cases of otherwise apparently moderate severity, without such a febrile reaction on the part of the patient, often do badly or terminate unfavorably.

Bacteriology has perhaps produced the strongest evidence causing this widespread and radical change of belief as to the nature of fever.

It is a well-known fact that the *Micrococcus lanceolatus*, the *Bacillus anthracis*, and the *Bacillus tuberculosis* thrive best at the bodily temperature, and do not develop in the usual way at 42° C. Indeed, the virulence of the first two is distinctly lessened from exposure to this temperature.

Ordinarily fowls are not susceptible to anthrax; but it has been found that, if their temperature be reduced in various ways, they become infected and succumb to the disease.

Further, rabbits kept in a warm chamber at 40–42° C. are able to resist infection with the pneumococcus, but become infected when taken out. Control animals at the room-temperature perish in a short time when inoculated with the same organism (Walther).

Cooling rabbits artificially increases their susceptibility to the pneumococcus, and they perish before others kept as controls at room-temperature. Similarly artificial elevation of bodily temperature by keeping rabbits in a hot box prolongs life after infection with anthrax and rabbit septicemia, while lowering their temperature in the same way shortens it (Rovighi).

So, also, Filehne demonstrated that rabbits infected with erysipelas in the ear show a rapid reaction of short duration, with speedy recovery, when kept in a warm chamber; while others infected in the same way at the room-temperature show a much more severe reaction, which lasts a long time, and they recover very slowly.

In the same way, rabbits with fever produced by cerebral puncture are able to live longer after infection with chicken-cholera, pneumonia, and swine-erysipelas than controls; they are able to resist an amount of toxin several times as great as that required to kill animals under ordinary conditions; the local reaction with erysipelas may be severe, but terminates in recovery (Löwy and Richter).

These experiments indicate that *the real danger in fever is not the pyrexia or elevation of temperature, but the poison causing it*; and that fever is, in a measure, like inflammation, a beneficial process, operating to protect the economy.

TERATOLOGY.

CLASSIFICATION.

TERATOLOGY treats of deviations from the normal in the development of the embryo. In a broad sense it treats of all malformations or anomalies of animal structure, from a slight variation like an anomalous artery, through the supernumerary digits, the meningoceles, the brainless monsters, the acardiac and amorphous fetuses, to the double and triple monsters. The word teratology is derived from the Greek *teras*, the equivalent of the Latin *monstrum*, meaning portent. The birth of a monster was anciently considered an omen of woe and portentous of calamity.

A satisfactory classification, in the present state of our knowledge, cannot be made. It is not yet possible to divide all malformations into classes according to etiology alone, although the best attempts are along that line. The early classifications were according to external appearances and dissection. Buffon, one hundred years ago, suggested dividing human malformations into those by excess, those by defect, and those by altered form. This classification, however, is incongruous, throwing together such widely different conditions as supernumerary digits, giants and double monsters, hypospadias, dwarfs, and acephali. Vrolik declared that classification was not possible beyond the merest convenience in grouping.

An article on teratology would be incomplete without some consideration of the system of classification elaborated by St. Hilaire in the third decade of the nineteenth century. His scheme was based upon external shape; and, since malformations allied as to external shape have often a similar etiology, a classification based upon such characteristics is not entirely unscientific. His plan is the basis of all later ones and is still extensively followed in teratologic literature. According to his scheme, all vertebrate malformations can be embraced in four great divisions: *Hemiteratic*, *heterotaxic*, *hermaphroditic*, and *monstrous*.

The **hemiterata** include all anomalies of structure not of the specific character of the hermaphroditic or heterotaxic malformations, nor yet grave enough to be classed with the monsters. Of course, here, as elsewhere in natural science, dividing lines are indefinite. The line between anomalies such as the hemiterata and true monsters may be roughly determined by the consideration whether the malformation is compatible with a continued existence of the affected individual in a manner not essentially different from that of his fellows. Thus, a man with digits deficient in number might live a life nearly normal, while one having the shortened limbs of a phocomelus could fill only a very restricted scope of existence. Among the hemiterata are the anomalies of volume, as dwarfism and giantism, of local smallness or bigness; anomalies of form, as crooked noses or the congenital deformities of the pelvis; anomalies of color, as albinism or melanism; anomalies of structure, as defective or excessive calcification of bones;

anomalies of disposition of organs, such as herniæ, club-foot, aberrant blood-vessels or muscles, imperforate canals, unclosed clefts like harelip; anomalies of number, as supernumerary breasts or defective number of digits or the existence of a tail, which last means merely an excessive number of coccygeal vertebræ.

Heterotaxis embraces all cases of inversion of organs or parts of the body. There may be a complete *situs inversus viscerum*—that is, a condition in which all the organs are transposed as to the sides of the body; or there may be a less general transposition, involving only the situation of the heart on the right side, the liver on the left, or a wrongsided position of one or more organs. Usually more than one organ is involved, and more often in the abdomen than elsewhere. With visceral transposition there does not necessarily or even usually exist also lefthandedness. Transposition will be considered further in connection with homologous twins.

Hermaphroditism includes all the varieties of amphimorphism of the external and internal genitalia.

Monsters are of course the most numerous and interesting division, in St. Hilaire's system. He classifies them according to external form and is needlessly explicit in his fine distinctions, but in the main his grouping is convenient. He has at least given us a useful working terminology which even to-day can be followed with advantage.

The classification of Ahlfeld, which will be followed in the main, retains much of that of St. Hilaire, but arranges the different orders and species more according to their proved or probable causes. He first considers splitting of the undifferentiated embryo, resulting in composite monsters, double or triple. In the first division of this order are included cases of complete splitting, the homologous or uniovular twins (and triplets), the allantoic and included parasites, and twins joined at the thorax, umbilicus, or cranium. In the second division of the order of double monsters he includes those in which the duplicity is only partial, involving only a portion of the cerebrospinal axis; such are the dipygi, syncephali, ischiopagi, pygopagi, and rhachipagi. The other order includes all the single monsters and anomalies. The first division embraces those anomalies and monstrosities due to the splitting of the embryonal area of single parts, members, or organs, producing supernumerary or accessory parts. Another division includes those anomalies due to nonclosure of the anterior and posterior commissures of the body, a numerous and well-marked class. Lastly there are various small classes not included in the foregoing and due to causes sometimes undetermined.

TERATOGENESIS.

Teratogenesis, or the theories of the origin of anomalies, malformations, and monsters, may be classed as superstitious and scientific. We should like to be able to say that the theories of the former category belong entirely to the dark ages of medicine and to the period before the revival of letters. It is astonishing to note, however, that some are held even to-day by medical men. One reason why we find so few recorded cases of monsters in the classical literature is because such infants were almost invariably destroyed at birth, being considered evidences of the wrath of the gods. In the Middle Ages, Satanic influence, either by direct cohabitation or indirectly, was thought

to be a frequent cause of monstrosities. Sometimes, especially when in the eyes of witnesses the monster very strongly resembled an animal, bestiality on the part of the woman was made to account for the case. In Copenhagen, in the sixteenth century, a girl was burned at the stake for bearing a fetus which resembled a dog, probably an anencephalus. The superstitious element is still seen in the present common law, by which a monster may inherit if it resembles the human form, and not inherit if it resembles a beast.

The superstitious idea as to the causation of monsters which has resisted the influence of reason the longest, and which is still held by perhaps the majority of medical men in this country, as well as almost every layman everywhere, is that nervous or mental impressions of the mother, occurring during pregnancy, in some mysterious manner react upon the growing embryo so as to cause it to undergo some kind of malformation.

Not only monsters, but even the common pigmented spots, moles, and nevi, are popularly supposed to be the results of maternal marking. The course of reasoning usually is that first the anomaly is observed, and then something is sought in the history of the pregnancy to which the anomaly may be ascribed. Great ingenuity is often displayed in ferreting out some fright or mental shock as the cause of the phenomenon. Since anencephali are by far the most common of monsters, and since, from the lack of cranium, their foreheads recede abruptly above the eyes, thus giving the appearance of the head of some animal, like a dog, cat, or frog, it is usual to find in the history of the case that the mother was frightened or shocked by seeing such an animal under frightful circumstances. The literature is full of reports of cases in which maternal impressions were supposed to have caused anomalies, but the maxim *post hoc ergo propter hoc* applies in nearly all. The time in the pregnancy seems to be immaterial; the same sort of malformation is often reported to have been caused in different cases at various periods of gestation. The arguments in favor of the influence of maternal impressions rest entirely upon the fact that in a large number of cases anomalies have followed nervous shocks inflicted during pregnancy, or that, after the birth of a fetus abnormal in some particular, it has been possible to discover a story of such shock. No experiments have ever been recorded by competent observers.

In the first place, the theory of maternal impressions should explain all cases. In most, in spite of diligent search, no event can be found to account for the particular anomaly under consideration. Conversely all cases of fright or nervous shock during pregnancy should be followed by the birth of a monster, or at least of an anomalous fetus. Comparatively few women go to term without at some time having had a mental shock or fright as great as many of those reported as producing abnormal fetuses, but monsters and anomalies are comparatively rare in the number of children daily brought to the light. How also shall anomalies be accounted for in internal organs, of the existence of which the mother perhaps did not know? Most malformations involve either an excess or a deficiency of tissue. It is hardly conceivable that a mental impression of the mother could remove structures already formed. Thus, the sight of a one-eyed man at the middle of pregnancy could hardly cause one of the eyes already formed to disappear, leaving only one, and that in the middle of the forehead, as in Cyclops. Yet we know that the eye-vesicles begin to bud out from the cerebral vesicles, one on each side, during the first fortnight. So in most malformations the organ

or part under attention is usually far on in its development and beyond the reach of any deterring influence during the early weeks or even days of gestation, while most of the recorded maternal impressions occur late in pregnancy. If it is hard to conceive how the mental condition of the mother could remove any part of the embryo, it is even less conceivable how it can add anything. How can the redundant anomalies, the supernumerary organs or digits, and especially the double monsters, be accounted for by the theory of maternal impressions?

The mammalian or even the human ovum, except for nutrition, is really as much outside of the influence of the mother's body from the moment of its escape from the ovary as is the egg of fowl or fish. The placental villi commingle with the greatest intimacy with the glandular tissues of the uterus, but at no time or place does the maternal tissue coalesce with that of the fetus, nor even does the mother's blood reach the veins of the offspring. Even supposing that nervous stimuli could pass from uterus to placenta, how could they reach the fetus through the umbilical cord, which is known to be devoid of nerve-fibers?

Numerous experiments have been performed upon the eggs of birds and lower animals, which have resulted in producing all the typical varieties of monsters, especially the single ones. Malformations are artificially produced in the embryos of birds, identical with those in man that have been ascribed to the influence of maternal impressions. As we shall see in considering the etiology of different malformations, most of them can be ascribed to perfectly definite physical and mechanic causes entirely dissociated from psychic influence.

For almost all forms of anomaly or monstrosity a scientific cause has been found, and for those still undetermined there is reason to believe that a rational cause will at some time be found. The occurrence of malformations can be explained mostly by the action of physical forces external to the embryo. Double formations arise from fission of the whole or a part of the original embryonic cell-mass. This fission occurs either from a superabundance of germinal material in the original embryonic area, or from constriction upon the embryo by the zona pellucida, or upon a combination of both causes. The action of abnormal amniotic bands and the adhesions of the overlying amnion to different parts of the embryo are potent factors in the production of single monstrosities. In the amnion we have a membrane resembling peritoneum and doubtless subject to the effects of irritation, inflammation, and vascular changes that would cause more or less cicatricial contraction and more or less adhesion of different parts of the membrane to other parts or to the surface of the embryo underneath. Occurring at different periods of the embryonic development, these abnormalities of the amnion give rise to vastly different results in the final outcome of the monstrosity. Folds or bands lying within clefts and openings which normally close at a later period may cause various abnormalities from incomplete closure at the proper time or at all. That such amniotic bands and adhesions are seldom seen at the birth of the fetus is weak argument against their former existence, because such is the developing and restorative power of embryonic tissue that it is very easy for the amniotic cause to have disappeared, although leaving a monstrous condition in the fetus as a result of its former presence. We may speak with truth of arrested development as a frequent cause of fetal anomalies. We must remember, however, that the

cause of this arrested development itself is some mechanic hindrance to the ordinary course of embryonic life. This mechanic hindrance is usually found in amniotic bands or adhesions. Some are due to circulatory disturbances or other factors that cause dropsic enlargement of internal organs, such as the brain or abdominal viscera, and consequent nonclosure of the dorsal or ventral commissure of the body. There still remain some abnormalities which must be ascribed to arrested development alone, because the ultimate cause of the arrest cannot be determined. Atavism has been invoked to explain some few anomalies: such, for instance, as the existence of a tail, an excessively large appendix vermiformis, and perhaps supernumerary digits. The presence of a caudal appendage is probably the result of persistence of an embryonal structure.

DESCRIPTION OF VARIETIES.

Compound monsters are those in which there are present to a greater or less degree the parts or organs of more than one individual. Since there is only one perfectly authentic case on record of a monster more than double, it will be sufficient to consider compound monsters as merely double. There is always regularity in the direction and extent of the duplicity. There is never, for instance, a head at each end of the body, an extra limb growing from the occiput, or other such irregular junction of parts of two individuals. The cerebrospinal axes are always more or less divided; that is to say, there is always an approach to two individuals with axes originally parallel. The evidence of duplicity may be very slight, involving only the extreme anterior portion of the face or the tip of the tail, but always a portion of the cerebrospinal axis. Externally it may appear as if only the tip of the tongue were double; but, to be a true compound monster, there must be also a trace of duplicity in the bones of the base of the skull.

It was formerly considered that double monsters were due to the junction of two fetuses lying close together. This would be impossible with twins from two eggs. The chorions and amnions of the ova would prevent union; even if these membranes should coalesce, the presence of the amniotic fluid and the motions of the uterus and of the embryos within it would effectually prevent junction of the twins. Double monsters, the individuals of which differed in sex, have never been authentically recorded. If coalescence of biovular twins were possible, double monsters having one part male and the other part female would sometimes be observed. The fact that double embryos are always joined at identical parts is proof that they were not due to junction of two previously separate fetuses, because then the two embryos would sometimes be joined irregularly, such as head end to tail end, abdomen to dorsum, upside down, and the like. Such double monsters are never seen, although it may at first sight seem so in some instances of parasitic forms.

Though coalescence of biovular twins is almost universally denied, yet the possibility of the origin of compound monsters from so-called double-yolked eggs must be considered. In birds' double-yolked eggs, hatching sometimes occurs; although rarely are two embryos formed, and never double monsters. There is no ground for believing in the existence of an *ovum in ovo* among mammals. A double-yolked egg of a bird merely means

that two yolks, which alone are the analogues of the mammalian ova, have entered the oviduct close together and have become enveloped together in the white membranes and shell. An avian double-yolked egg is essentially two ova, and cannot be compared to any condition obtaining among mammals. Authorities are nearly unanimous in holding that all double formations arise from one ovum.

Assuming, then, that only one ovum is concerned in the formation of double monsters, we are confronted by two theories as to their formation from the one egg. One holds that they arise from splitting of the germinal area of one embryo, and the other that they arise from the fusion more or less of two distinct embryonic areas lying in one ovum. These are the fission theory and the union theory. By the former the embryos are supposed to have been originally one, and to have split into the parts of two embryonic areas; by the latter they are supposed to have been double from the beginning, and to have become more or less joined together. It is certain at least that the fission or the union of the embryonic area or areas takes place at a very early period, long before any differentiation of the cell-mass has begun. In the bird's egg this is probably before the egg has been laid. While the question is still far from determined, and while either solution will give a working basis for classification, yet the largest number of the best authorities favor the fission theory. The advocates of the union theory claim that the circumstance whether the blastoderms lie near or far from each other on the surface of the ovum determines the union or the complete independence of two embryos. The first would claim, for instance, that homologous twins arise from a complete splitting of the embryonic cell-mass; while the second would claim that the diprosopi or the double-tailed monsters arise from a complete fusion of the embryonic cell-masses of a pair of homologous twins.

All uniovular twins and the two halves of double monsters are usually very much alike—physically, mentally, and morally. The fission theory explains all the varieties of double formations, from homologous twins to duplex digits. The amniotic fold which was the cause of the fission of the anlage of a duplex thumb has been found persisting between the portions of the duplex digit. A strong point in favor of the fission theory is that the union is always, even in parasitic cases, at an identical point in each portion of the monster. Except in the cases of included fetuses, the union is always by the longitudinal axis of the body, and the poles of the two portions of the monster correspond. Again, the anterior or cephalic end is the larger in the embryo; and therefore, if two embryos unite, we should expect that end—approaching, on account of its size, nearer to its twin—to be more frequently united with the latter. On the contrary, the union is more often at the caudal end. Observation and experiment are limited in respect to beginnings, in the history of double monsters. The earliest double human embryo is of four weeks' growth, and the earliest double hen embryo twenty-four hours; both too old to allow study of the formation of the double germs. This is best studied in the eggs of fishes, amphibians, and echinoderms, which lend themselves more readily to observation and experiment.

Twin births, to a certain extent, run in families. It seems as if the eggs of certain women had an excessive amount of embryonic material, or that such women produced more eggs. The author has personal knowledge of a woman who has produced two pairs of apparently uniovular twins. It seems that

for homologous twins and double monsters there must be at a given period an excess of constructive material over that required for the same period in a single embryo. Polyspermia, the condition of two spermatozoa gaining entrance to one ovum, might perhaps be thought to influence the production of double embryos. While it is possible for two spermatozoa to enter one ovum and even go so far as to produce two male pronuclei, yet such polyspermious eggs whenever observed always blast very soon afterward, even before the segmenting stage. Such observations have been made and controlled experimentally in the eggs of frogs and fishes.

Although double-yolked eggs in the true sense cannot exist in mammals, yet binuclear and polynuclear eggs have been considered evidence in favor of the union theory. These so-called twin eggs have long been observed in the primary follicles of the ovaries of mammals and even of the human species. Although segmentation of the primordial ova of man had been denied, yet Schultze saw, in a four months' embryo, marked increase of these ova through mitosis. Double-egged primary follicles have been observed by others, and also double-nucleated eggs in the newborn and even in children of few years. Nagel takes these to be true twin eggs and considers that twin embryos may develop from such. Up to 1899 the oldest girl in whom polynuclear eggs had been observed was four years of age. Von Franqué reports that he has seen, in the ovary of a girl of fourteen years, numerous primordial eggs with two, and one with three, nuclei. Also, he is the first to report the existence of a binuclear ovum in the ovary of an adult woman. The ovaries of a woman of thirty-five were removed for cystomas. In one ovary he found a follicle containing an egg which had two nuclei, each containing a germinal spot or nucleolus. The egg appeared normal in structure and development. He concludes that this was a true twin egg and that from such are developed uniovular twins.

Of course the latter conclusion does not necessarily follow. In the first place, it is not certain that the embryo develops from the nucleus or so-called germinal vesicle. All we know is that the male pronucleus derived from the spermatozoon approaches, within the ovum, and joins the female pronucleus, which is not proved to be identical with the germinal vesicle. Even were it so, still it is not proved that the spermatozoon divides to fertilize both female pronuclei, or that two spermatozoa enter double-nucleated eggs. So far, only one observation has been made of a polynuclear ovum in an adult, and yet we know that uniovular twins are relatively not rare. It is perfectly reasonable to conclude that double nuclei in the ova of mammals merely mean the segmenting and consequent increase of ova. If double-nucleated or so-called twin eggs develop usually into uniovular twins, we should expect, on account of the relative frequency of the latter, that such eggs would be found with equal frequency in the ovaries of adult women.

If further observation shall disclose that the occurrence of binuclear ova in the ovaries of sexually mature women is relatively as common as the occurrence of uniovular twins, or if observation proves that a double embryo or two embryos have developed from such an egg, it will be necessary to believe that from such twin eggs may arise homologous twins and double monsters. All appearances indicate that these double embryos and twin embryos arise in eggs which have a superabundance of formative material. Prolific women are more apt to bear homologous twins, and it may be that the primordial ova of such women have segmented and increased more than

commonly, so that there is an excessive amount of nuclear material in the ova, even to the extent of the existence in some ova of two nuclei. Perhaps the female pronucleus is formed in these twin eggs from the two nuclei or germinal vesicles, and therefore becomes unduly large, so that in the embryo an excessive amount of embryonic material is provided, which gives rise to two embryos or to a double embryo.

That fission of the embryo is possible from mechanic force has been



FIG. 139.—Duplex formation in frogs (O. Schultze).

proved by O. Schultze's experiments on frogs' eggs (Fig. 139). He produced double monsters by holding eggs between glass plates and turning them at different angles during the segmentation stage. Fish eggs carried far in railroad-cars and other vehicles, and thereby subjected to considerable shaking, show a much greater percentage of double formations than eggs hatched without such agitation. It has also been found that more double monsters develop from fish eggs hatched in running water than from eggs of the same species and under similar circumstances hatched in still water. Various mechanic causes may act in producing the very early splitting of the embryo so that a double monster is produced.



FIG. 140.—o, Blastodermic vesicle; e, Primitive germ; z, Zona pellucida (Ahlfeld).

In mammals the splitting of the embryo is probably very often due to constriction of the zona pellucida upon the embryo underneath (Fig. 140). There is perhaps a disproportion between the germ and the zona pellucida. Perhaps the excessive amount of the embryonic material causes the cell-mass to project unduly above the surface of the ovum. This causes the zona pellucida to be stretched more or less tightly over the germ, and there-

fore to cut through the cell-mass of the underlying embryo. This occurs at a very early period, even before the formation of the primitive groove. In fact, this splitting of the embryonal anlage takes place before the cells have been at all differentiated, shortly after the completion of segmentation. Then, either because there is excessive amount of embryonic material in the embryonal anlage or because the zona pellucida is unduly small, there ensue a pressure and a stretching* of the enveloping membrane, which gradually cuts into the embryonal mass, causing it to develop doubly, in whole or in part, according to the extent, direction, and situation of the splitting.

If the fission has been complete, the two halves will lie parallel and will slip down on the blastoderm away from each other, while the yolk-granules from below are forced upward between the two embryos. If the fission has been only partial, then the split portions will slide down the blastoderm and be separated by the yolk-granules, while the united portion remains in its former situation. In all double formations and homologous twins, the sex is female twice out of three times, but always identical in both portions.

The most probable cause, then, of double monsters is splitting of the very early embryo into two parts, partially or wholly separated. They arise from one ovum and from one impregnation. Their classification is based upon the extent and direction of the splitting.

Homologous Twins.—When the splitting or the separation of the undifferentiated embryonal anlage is complete and the two portions of the embryo go on to perfect development, there are born the so-called homologous or uniovular twins. While, in the autositic stage they can hardly be called monsters, and would probably themselves resent that title, yet their mode of origin is doubtless the same in kind as that of true double monsters. Uniovular twins are always of the same sex and are always much more alike in bodily appearance, mental characteristics, and even moral nature, than are biovular twins. Of course, the resemblances are most marked at birth and in very early childhood. After they go about separately in the world and are subjected to different environment, each acquires peculiarities of his own; but throughout life, and even to advanced age, there persists a remarkable unanimity of appearance and thought. Homologous twins are not rare. Of 506 twin births examined as to the membranes, 444 were proved to be double-egged and 62 single-egged; therefore, one twin birth in seven is uniovular. Twin births in general occur about once in 100 labors; therefore uniovular twin births occur once in 700 labors.

Uniovular twins can be recognized at birth by the existence of but one chorion. There is almost always only one placental mass, and the allantoic vessels usually anastomose more or less with those of the fellow-twin. This anastomosis is sometimes a serious or even fatal matter to one of the twins. Homologous twins are very likely to have the same diseases and especially the same congenital anomalies. The latter phenomenon may be explained by the fact that they usually occupy the same fetal membranes and so are subject to the same results of diseases of these membranes. Thus, if spina bifida or nonclosure of the abdomen occur in one, it is likely to occur also in the other.

Parasitism in Homologous Twins; Acardiacus.—We have so far considered the autositic uniovular twins; in other words, those of development equal throughout gestation. Their parasitic varieties occupy the realm of

real monsters. Up to about the twelfth day, the two embryos develop evenly. At that time the allantois buds out from the hind gut of each individual, and its vessels reach the placental portion of the chorion. Sometimes the allantoic vessels and later the placental vessels anastomose too freely with those of the other twin; then begins a contest of the two fetal hearts, as to which shall dominate the circulation. One fetus, from its more favorable situation or other cause, overcomes the force of the other's heart in the anastomosing vessels, and thereby is caused a stasis in the arteries of the weaker fetus, progressing inward from the anastomosing allantoic arteries. Finally the force of blood-circulation is entirely overcome in the body of the weaker fetus, and it dies. The increasing growth of the surviving twin with its appendages gradually compresses the dead one and finally squeezes it flat against the uterine wall, so that the *fetus papyraceus* results. Other causes of the early death of one twin may also bring about such a deformed fetus. The twins are not necessarily homologous, but the foregoing is by far the usual process in the production of the flattened fetuses. Unless careful search is made among the membranes and clots, such flattened fetuses, especially if the death occurred early, may be overlooked at the birth of the live one (see transposition of viscera in homologous twins).

The true allantoic parasites arise in a similar manner. Two healthy



FIG. 141.—Schematic representation of the development of the pure allantoic parasites (Ahlfeld).

embryos develop from one egg, as in ordinary cases of homologous twins (Fig. 141). The allantoic stalk of one may reach the inner surface of the primary chorion a few hours or so before that of the other. It becomes attached to the chorion here and begins to develop its umbilical vessels before the second allantois reaches the placental site. Therefore the allantois of the second embryo finds no chorionic attachment or only a limited one, and is compelled to attach itself to the allantois of the first. There results an anastomosis of the umbilical vessels, and the first fetus becomes dominant in the circulation. As the allantoic stalks become lengthened out into umbilical cords, the cord of the second may be attached to that of the first at some distance from the placenta; it may be attached to the placenta close to that of the first, or the two may be connected by a large vessel upon the placenta. The anastomosing arteries leading to the second will carry all or nearly all of the blood directly from the circulatory system of the first, without going through the placenta. The venous current, being slower, will not follow the line of least resistance so markedly. The second embryo, therefore, gets arterial blood—that is, vitiated blood—from the first embryo's body. Also the blood-pressure from the heart of the first forces the current backward through the arteries of the second. The embryonic heart of the latter atrophies. The current is more direct from the umbilical arteries

toward the lower parts of the fetus by way of the hypogastric arteries than toward the head; in fact, the hypogastric arteries become the important vessels of the parasitic fetus. The organs normally receiving blood direct from the heart, such as the lungs, head, liver, etc., become atrophied or fail to develop at all. The distance from the heart of the autosite, which is the only pumping force in the bodies of both fetuses, is great; therefore the circulation is weak in the parasite's vascular system. On account especially of the stasis in the veins, there is usually a hypertrophy of the connective tissue, especially of the skin, and a general edema of the subcutaneous cellular tissue. According to the degree of the development of the



FIG. 142.—*Acephalus acardiacus dipus*.

allantois and placenta of the second embryo, we get several varieties in acardiac fetuses.

Acardiacus anceps is the least atrophied form, and is characterized by absence or nondevelopment of the face, the extreme anterior part of the body. There are rudiments of cranial bones and of the brain. The species is rare.

The most common species is the *Acardiacus acephalus*, in which the whole head is wanting or very rudimentary (Fig. 142). Sometimes there is found a little rudiment of cranium, and often a few hairs are seen upon the extreme cephalic end. Dissection usually shows the intestines and abdominal organs rudimentary, and the organs above the diaphragm are represented by the merest trace. There are rarely more than a few vertebrae,

and these are usually of the lumbar or sacral type; the shoulder-girdle is undeveloped, but the pelvic bones and those of the lower extremities are more nearly perfect.

The least developed form of acardiac monster is the *Acardiacus amorphus* or *anideus*, which is little more than a lump of connective tissue covered by edematous skin, sometimes bearing a few hairs. There is usually some attempt at budding-out of limbs, but these seldom have any systematic bony structure. A few pieces of bone may be found inside the body, and there may be some rudiments of visceral tissue.

The rarest acardiac monster, and indeed the rarest of all monsters, is the *Acardiacus acornus*, a fetus with head alone. Even the head is never fully developed, usually lacking some portion of the cranium and much of the brain. The genesis of this form of monster is very obscure, but the anastomosis of the yolk-vessels at the lower surface of the embryonic heart might account for the development of the head while the rest of the body remained undeveloped from malnutrition. The only representative of the body is a sac under the head, closing off the neck. In no case has an acornus been known to have an umbilical cord, but the head hangs to the placenta of the normal twin by means of the membranes. There is not sufficient evidence to judge whether or not the monstrosity is due to persistence of the vitelline circulation.

The *included fetuses* are the second class of parasitic twins. In some cases they may be due to attachment of the delayed allantois—not to the allantois of the autosite, but to some part of its body—and final partial or complete inclusion of such parasite within the body of the host. There is no umbilical cord running to such parasites, and they receive their nutrition from the anastomosing vessels of their hosts. The type of such fetuses is illustrated by the *Epignathus*, which is an acardiac amorphus which is joined to the autosite at the mouth, usually at the hard palate. It may be only a small tumor in the roof of the mouth or a huge pedunculated mass hanging out of that cavity. It is composed of numerous cysts which contain mucoid matter and sometimes brain-tissue, also rudiments of limbs and various organs. The *epignathus* arises because one of a pair of homologous twins is smaller than the other and lies near the head end of the larger twin. As the cephalic fold of the amnion of the autosite is folded downward as the head bends down, it carries with it, lying on the surface of the ovum in the near neighborhood, the whole of the smaller embryo, which thus becomes folded into the oral cavity or pharynx of the host (Fig. 143). Why one of the twins is smaller than the other can only be conjectured; perhaps, at the time it split off from the rest of the undifferentiated anlage, it was only a small portion of the mass. In the eggs of frogs it has been observed that small pieces of the egg will sometimes segment and develop like the larger part, differing only in size from the other embryo. It is conceivable that a minute por-

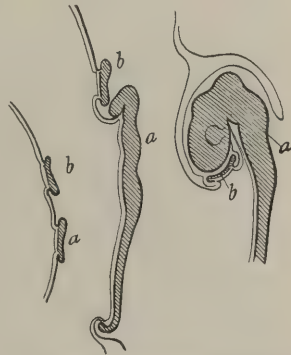


FIG. 143.—The inclusion of one embryo within the cephalic fold of the other (Ahlfeld).

tion of the undifferentiated cellular mass was pinched off by the overlying zona pellucida and detached from the larger twin-mass, afterward becoming included as above described. In a similar manner a smaller embryo may be included in the sacral region of the large twin, or in the abdomen or other part of its body where included fetuses have been found. The theories as to the origin of dermoid cysts and teratomas are discussed in another part of this work.

Double Monsters.—When the splitting of the embryonal cell-mass has not been complete, as in homologous twins—or, if we accept the union theory, when two embryos lying upon the same blastocoele coalesce in part—we have the formation of double monsters in the restricted sense. These may be conveniently divided, according to the extent and direction of the duplicity, into Katadidyma, Anadidyma, and Anakatadidyma.

Katadidyma.—The *Terata katadidyma* are characterized by duplicity extending from the cephalic toward the caudal end, or, speaking of the human fetus, from above downward. This duplicity has all the grades, from the slightest, where there is little more than a double tongue, to the greatest, where there are almost two distinct individuals joined only by the nates and the tip of the coccyx. The Katadidyma may profitably be divided into four genera, according to the extent of the duplicity.

Diprosopus.—This genus is distinguished by a body apparently single and a head single caudally but more or less double as regards the face. A double tongue would hardly be considered to mark duplicity; but if on dissection there is found a double condition of the anterior cranial bones, such would be considered the case. In some diprosopi the facial axes are nearly parallel, in some convergent below, and in some convergent above. The genus is divided into species, according to the number of eyes and of ears: in other words, according to the extent of the split; because the more extensive that is, the more room there is for eyes and ears. Therefore diprosopi are distinguished as *diophthalmus*, *triophthalmus*, *triotus*, etc. A constant characteristic is the existence of a single neck, because the duplicity does not extend below the cranium.

Diprosopus is relatively rare in man, occurring in about 6 per cent. of double monsters. The sex is female two-thirds of the times. It is most common in calves and kit-



FIG. 144.—Dicephalus.

tens. In a large number of human cases, anencephalus exists also. Partly because of this, and also because of the necessary defectiveness of the brain and the mouth which interferes with nutrition, these monsters are seldom capable of independent existence, although viable cases are on record. I have seen a case in an adult cow.

Dicephalus.—This form is characterized by the existence of two distinct heads with some splitting of the cervical spine even in the slightest cases. The genus is divided into species, according as the divergence of the spinal column is great enough to allow the development of two, three, or four arms, or of a third leg. Thus the species are called *Dicephalus dibrachius*, *tribrachius*, and *tetrabrachius*; also *Tribrachius tripus* and *Tetrabrachius tripus*. In all double monsters, as a rule, and especially in dicephali, there is a right and left symmetry of the internal viscera as far as the duplicity extends.

The two-armed species has only one thorax and abdomen and one shoulder-girdle; one heart (sometimes partly duplex); one pair of lungs (sometimes atelectatic rudiments between the normal ones); usually two stomachs and two gullets, but a duodenum which unites before the middle of its course. Where the separation is greater, as in the three-armed and four-armed species, there are two sets of ribs, with a sternum posteriorly, half of which belongs to each head. The greater the separation, the more likelihood that there will be two hearts or a heart markedly duplex. There is a common pericardium.

A famous case of *Dicephalus tetrabrachius* dipus was born in Sardinia in 1829, and was baptized Ritta-Christina. The fetus presented by the heads, which were delivered one after the other without much difficulty. The heads, arms, and upper portion of each thorax, to a point a little below the mammæ, were separate and normal. The ventral surfaces were directed somewhat toward each other. If the right leg was pinched, only Ritta felt it, and Christina alone felt a pinch on the left; while at points near the median line, such as the abdomen, anus, and genitals, the sensations were common to both. The two heads cried and laughed, ate and slept, often at different times. Ritta caught a bad cold from which she never recovered, and died at the age of seven months. Christina, who had been sleeping peacefully for some time before her sister's death, suddenly sighed deeply and expired without warning. The autopsy showed only a rectum filled with feces and slight inflammation of the lungs of Ritta. It was found that her heart was compressed by that of her sister, and that fact probably accounted for her succumbing to a slight obstruction in rectum and lungs. Both hearts, which were rights and lefts, lay in the same pericardium, and in life beat synchronously. When that of Ritta stopped beating, that of her sister was of course interfered with and stopped. In double monsters, each part dies within a short time of the other.

Dicephalus is the commonest double monster in mammals, but is rarer in birds. In man, one-third of all double fetuses are dicephali. The sex is female twice out of three times.

Ischiopagus.—The distinctive feature of this genus is the existence of two bodies, with the pelves united in such a way that the pubes of one joins the pubes of the other in the median line. The bodies are separate above the navel, thus allowing two abdomens and two thoraces. The species is distinguished by the number of legs—two, three, or four. There are also various asymmetric and parasitic forms. The typical form, *Ischiopagus tetrapus*, contains the whole of two individuals united as to their pelves. If split through the pubes and separated, and the pubic regions united each to its own, two complete individuals would be formed. The union is typically at the tips of the coccyges. It is usual to have some malforma-

tion of the external genitals and atresia of one or both of the rectal openings. For this reason and because they are commonly born prematurely, it is rare for ischiopagi to live more than a few days. None are reported living more than one year. The monstrosity is much less common than dicephalus. Females predominate.

Ischiopagus Parasiticus.—Both sides of a double monster may be unequally developed, so that one portion appears as a parasite of the other. In ischiopagi, the head—or head and trunk—of one twin may be wanting. *Ischiopagus dipygus*, or double-buttocked, may be explained as follows (Fisher). We will imagine that the head and trunk and arms of one fetus are missing; then imagine that the two legs belonging to the parasite are drawn down until they are fused along their inner sides. Thus we have an individual with one normal trunk and upper extremities, two normal legs, and between them a compound leg, on either side of which is a set of external genitals. The dorsal aspect of the compound foot is turned forward, and the species is thus distinguished from the *Dipygi* proper, which will presently be considered. A unique case of this kind is that of Jean Baptiste dos Santos, born in Portugal in 1846, and perhaps still living. One picture shows him as an infant one year old, with a well-developed body and outside legs, and a compound leg between the others. The foot is double and the toes turn backward. On either side of the compound leg is a scrotum containing a testis; above the third limb are two smaller pouches, each of which contains a testis; these last went back into the abdomen later in life. Another picture represents him as a young man of twenty-two. He was able to hide his deformity under his clothes by strapping his extra limb to one of the others. He could use both penes in coitus, but preferred the left.

Pygopagus.—In this genus of the Katadidyma, the splitting from before backward has reached the maximum. The union is usually at the sacrum or coccyx, and might perhaps allow the name *Rhachipagus* to be given to the genus. The vital organs in the typical and symmetric form are distinct, although the rectum and the external genitals are sometimes more or less fused. In females the vaginae are usually separate, but there is a common vulva; in males there is usually one scrotum containing four testes, and the penis is single. The symmetric or autositic form is rare, both in man and animals; but parasitic varieties are common, especially among fowls. Since the vital organs are usually well formed and independent, the pygopagi are generally viable and may attain advanced life.

The most famous case of symmetric pygopagus is that of the Hungarian sisters, Helen and Judith, born in 1701. Helen first presented by the vertex and was delivered as far as the navel. After a delay of three hours the rest of the body passed, and then the body and head of Judith in reverse order. Some such mechanism as this is the common method in the birth of most double monsters. Menstruation came in each at different periods; they urinated separately from different urethrae; but, having a common rectum, they both felt at the same time the desire to defecate; the vulva and beginning of vagina were common, but the genitals above that point were distinct. They died at the age of twenty-one, from Judith's disease of the brain and lungs. The vertebral columns were fused from the second sacral vertebra to the tip of the coccyx.

The North Carolina twins, Milly and Christine, born in 1850 and still

alive as far as known, were similar in most respects to the Hungarian sisters.

Some of the forms of parasitic pygopagus depart so far from the typical that their place in classification is dubious, some being little different from the sacral inclusions. A rather common form is that of the so-called Italian three-legged boy. He has an extra leg which seems to be attached to the sacrum of the normal body, making him a *Pygopagus tripus*. Extra limbs attached to the rump are relatively common in animals, and especially so in fowls.

Anadidyma.—The *Terata anadidyma* are characterized by duplicity extending from the caudal toward the cephalic end. This duplicity is of all degrees, from mere splitting of the tip of the tail to the craniopagi, in which the junction is only by the tops of the heads. The division of this order into genera depends upon whether or not the duplicity involves less than all



FIG. 145.—Dipygus (pig).

the vertebræ or extends to include the cervical region or to involve the head.

Dipygus.—After the double-tails come the dipygi, in whom there is more or less of a double condition of the pelvis. According to the extent of the doubling, there will be room for a number of legs; and thus the species are distinguished, as *Dipygus dipus*, *tripus*, and *tetrapus*. In the more exaggerated cases there are two complete pelves bearing two complete pairs of legs (Fig. 145). The slighter cases have but little tendency to duplicity of the pelvic bones, but have a double condition of the external genitals. Many of the diphallic individuals are double monsters. Dipygus is rare in man, but more common in lower animals. A famous case of *Dipygus tripus* is that of Blanche Dumas, born in 1860 and probably still living. The belly and pelvis are broader than usual; between the normal legs is a third, on either side of which is a set of external genitals. The only external points of difference between her and dos Santos, as an *Ischiopagus dipygus*, is that

the third leg is single and that its anterior aspect points forward like the normal legs.

A probably unique case of *Dipygus tetrapus* is that of Mrs. B., reported by Wells. The pelvic region was very broad, and between the two normal legs were two smaller legs placed symmetrically, with the external surfaces toward each other and the inner surfaces toward the normal limbs. There seemed to be two complete sets of genitals, both external and internal. There were also two anuses. She became pregnant in the left uterus, but labor was induced for incoercible vomiting.

Syncephalus (Fig. 146).—By some authors these are classed with the



FIG. 146.—Syncephalus.

thoracopagi having two heads and called *Thoracopagus syncephalus*. In this genus the splitting has extended up to the head and often involves it, allowing the existence of two complete spinal columns and two sets of ribs. The duplicity often extends so far forward in the cranium that there are rudiments of a posterior face or at least an ear. The thoraces are united by the ventral aspects, as in the four-armed dicephali. A complete sternum is developed on each side of the common thorax, half belonging to each twin. The chest-cavities are common or divided by a membranous partition; there is a compound heart or two hearts; the gut is usually double below the duodenum; the diaphragm is double. The brain is double posteriorly; there are two cerebelli, two pontes, two medullæ, and sometimes a double condition

farther forward. As in diprosopus, the duplicity and consequent mixing of the cerebral tissues probably account for the fact that these monsters rarely live long, even if born alive. On the contrary, the dipygi, having a single brain, though a more or less double body, are likely to live to adult age. The syncephalus is not a rare monster, and, like the other anadidyma, is especially common among lower animals.

Parasitism among the anadidyma is much rarer than among the kata-didyma; but among the dipygi and syncephali there are various examples of parasitic forms, in which one of the fetuses is more or less rudimentary.

Cephalopagus.—In this genus the bodies are entirely distinct and there are two heads, which may be joined at any point along the median line, from the occiput to the face. The point of union determines the species: thus, if joined at the cranium, the species is called *Cephalopagus craniodidymus*; if at the face, *protopodidymus*. The two heads are not always arranged with perfect regularity in respect to each other, since the faces may look in different directions. The genus, especially the symmetric form, is the rarest form of monster except *Acardiacus acornus*. Most of the genus is of the parasitic form, in which there is an extra head with only a rudimentary body or none (Fig. 147). Because of the independence of the organs, this monstrosity is not incompatible with continued existence. The most famous case was observed in Bengal in 1783, in the person of a child, having joined to the vertex of its head another perfect head without trace of body. During life, although no sign of intelligence came from the parasitic head, yet its eyes always filled with tears when the autosite cried, and pinching the skin of the extra head caused its face to assume an expression of pain. The child died at the age of five years, from the bite of a cobra. The brains were distinct and separated by dura. Only two human examples are recorded of cranial attachment at the frontal region, one of which lived ten years and the other eight months. One of the former twins died and was cut away from its fellow; but the latter soon died, perhaps from sepsis. The human examples of *protopodidymus* are all parasitic, and in most the parasite is very rudimentary. In one case the parasitic fetal parts were successfully removed by Prof. Pancoast.

Anakatadidyma.—In the anakatadidyma there is duplicity at both cephalic and caudal ends of the embryo, with union somewhere between, always involving the xiphoid region. The order is classified according to the extent of the duplicity, and therefore according to the amount of separation of the two halves. Following the general rule that, the more separate the brains and other vital organs in double monsters, the more likely are they to maintain a continued existence, we find that those forms like the



FIG. 147.—*Cephalopagus inodidymus parasiticus* (Dr. T. R. Williams, of Punxsutawney, Pa.).

Siamese twins, in which the union is only by a comparatively small band of tissue and in which the spinal axes are rather far apart, are most likely to live after birth. The genera of anakatadidyma are *Prosopothoracopagus*, *Thoracopagus*, and *Omphalopagus*.

Prosopothoracopagus.—In this genus the union is extensive and the separation small. The two vertebral columns, as in all of this order, are completely distinct, but lie so close together that the two halves of the compound individual are intimately united. Although this form resembles the syncephalus, yet in the former there is a distinct split of the extreme cephalic end of the embryo. The rudiments of the faces are on the same side. The esophagus, stomach, and duodenum are common, the air-passages duplex; there is a single heart, showing traces of duplicity. The genus is very rare.

Thoracopagus.—This genus is characterized by junction of the two portions at the thorax. As in the syncephali, the sternums are split and each half is united to the opposite half of that of the other twin. The chest-cavities are united, and are separated from the abdomen by a duplex diaphragm; there are two hearts or a duplex heart in one pericardium; there are four lungs; the gut is single from stomach to ileum. The genus is the most common of the equally developed double monsters. Rarer species are the *Thoracopagus tribrachius* and the *Thoracopagus tripus*, distinguished as indicated by the names. On account of the complexity of the lungs, livers, and hearts of thoracopagi, it is rare for them to live very long.

Thoracopagus parasiticus is very rare. A famous example is that of Johannes Baptista Colloredo, born in Genoa in 1617. His picture shows a smaller body attached to the front of his chest and hanging from him. This parasitic portion was ill developed, having only one leg and clubbed hands with only three fingers on each. The parasite took no nourishment and seemed to lead a purely vegetative existence.

In thoracopagi, as in most double monsters, there is usually or perhaps always a *situs inversus* of most of the viscera of the right twin. Normally the embryo turns over on its left side very early in development, so that the dorsum lies toward the left of the ovum. In the cases of double embryos, if the twins lie far enough apart to enable both to take the left-sided position, there will be no transposition of the viscera of the right twin. This condition obtains in the case of many homologous twins. When the two are united so that the right twin must lie with its back to the right, there will occur a transposition of the viscera in the right twin.

Omphalopagus.—The line dividing thoracopagi from omphalopagi is not definite. In the latter there is at least a connection between the tips of the xiphoids, and therefore a cartilaginous portion to the uniting band. This band usually contains peritoneum and a portion of liver. Sometimes there is a double insertion of the navel-string by a forking at the fetal end, but often there is only one cord inserted at the middle of the bridge. The so-called Siamese twins, born near Bangkok, Siam, of Chinese and Cambodian parentage, are perhaps the most celebrated of all double monsters. They lived to be sixty-five years old, married, had each a large number of normal children, and lived a very interesting history. In infancy they were joined by a band of flesh and cartilage extending from the xiphoid to the navel, so that their ventral surfaces were in apposition; but, as they grew and stretched upon this band, it elongated enough to enable them to stand,

sit, and lie, side by side. The question of separation by a surgical operation was several times considered, but almost all surgeons advised against interference. Perhaps now, with aseptic technic, such an operation might be successful; but the existence of a large band of liver in the junction would at least cause severe hemorrhage. Each twin had a normal set of organs, but there was a *situs inversus viscerum* in Eng, the right twin. The hypogastric arteries ran to both twins from the umbilical cord, which was inserted in the lower part of the middle of the bridge. Two or three other cases of omphalopagus are recorded, in one of which the band was successfully divided by a gradually constricting ligature.

Omphalopagus parasiticus is not so rare as the parasitic form of thoracopagus. The Hindoo lad Laloo is an example. He has a headless parasite attached to his umbilical and xiphoid regions. This parasite has two arms and two legs, with a rudimentary body between; no head. The parasite is purely vegetative, has no anus, but passes urine involuntarily.

Triple Monsters.—Homologous Triplets.—Uniovular triplets, like homologous twins, are always of the same sex and are very similar in appearance and nature. An acardiacus may exist in the same chorion with two normal fetuses, or two acardiaci with a single normal fetus. One or two cases have been noted of a double monster in the same chorion with a triplet. If the different forms ever occurred, it would be possible to classify triple monsters according to the extent and direction of the triplicity, as in double cases; but only one case is authentically recorded of a triple monster.

Tricephalus Dibrachius Diauchenos.—The obstetrician, confronted by a second head, and thinking that he had a case of locked twins to deal with, amputated the first, only to be confronted by a third. The first two heads were amputated and the third perforated before the child could be born. The placenta was single, but of twice normal size; there were two vertebral columns and three necks, two chest-cavities, two sacra, two ischia, four ilia, and two pubes. The pelvic contents were normal; the genitals were male and single.

Single Monsters.—Single monsters and malformations do not lend themselves so readily to classification as those of a compound character. In the latter there is probably one cause, varying in degree or place of action merely, while single abnormalities may be caused by many different factors, some of which are yet unknown. During the early weeks and days of embryonic life, the anlagen of the different parts and organs are being laid down rapidly and assuming their adult form. During the later months, these anlagen do little more than grow. Arrested development, as Ahlfeld says, is not a force, but a condition, and cannot of itself account for the production of anomalies. Some force, internal or external to the embryo, must be the cause of arresting the development at different stages. This cause cannot in all cases be determined, but must always exist, and in most cases can be recognized. The extent and anatomic situation of the malformation will depend upon the time of the interference, the extent of the interfering force, and the part of the embryo upon which the interfering force acts. The variations of these three factors will produce wide variations in the effects produced. Time is perhaps the most important element. The force is mostly the same, although varying in amount; but, even to the extent of a few hours, the time at which that force acts is a factor of the utmost moment in determining how great and of what kind the malformation shall be.

The persistence of embryonic clefts is a considerable etiologic factor in the production of malformations. The ventral and neural cavities of the body are formed by the union of ventral and dorsal clefts, the different parts of which normally close at different embryonic periods. The nonclosure of the different parts gives rise to different anomalies, varying widely in appearance. Important causes for hindering the closure of these embryonic clefts are: increased accumulation of fluid within internal organs, increased size of internal organs, prolapse of parts between the still divided margins of the clefts, the presence of amniotic folds between the edges, disturbance of the spheric curving of the edges so that they do not meet throughout, and lack of enough material to close the cleft. Behind all these causes is probably disease of the chorion, amnion, or uterus, or perhaps infectious disease of the embryo itself. Adhesions of the membranes to the embryo may in various ways interfere with the development of a part or obstruct its circulation, so that injury is done to some of the embryonic cells. The disease of the membrane may soon recover, because we know that the regenerative power of embryonic tissues is great; or the adherent band may atrophy and disappear, so that at birth no trace may be found of what was at the time a powerful cause of evil. The loss of a few cells in the early stages of the development of a part, or the delay of some phase of development even for a few hours, may have, in the later history of the intra-uterine life of the individual, results far-reaching and immensely important.

Amniotic bands and adhesions may compress limbs so as to deform or even amputate them, may bind fingers and toes together so as to make them webbed, may hold limbs in constrained positions so as to make them clubbed, may close normal openings like the anus, or in countless ways may give rise to deformities. Defective development from causes more or less obscure may result in general dwarfism, in cyclops, in symphus, and in ectromelus. Just as in twin embryos the cause may be an excess of embryonic material, so in giants and in local hypertrophies excessive development in single individuals may be due to superabundance of formative material not sufficient to give rise to splitting of the undifferentiated embryonic cell-mass.

Gastroschisis.—Nonclosure of the ventral commissure occurs in man, and perhaps in animals, more often than nonclosure of the dorsal commissure. Defects are seen at all points in the face, chest, and abdomen.

Prosoposchisis.—At the fourth week, in the middle of the face there is a large hole, bounded below by the primitive lower jaw, on the sides by the lower jaw and the ununited rudiments of the upper jaw, above by a continuation of the frontal with its two nasal processes. This mouth-hole connects above with the nasal and optic cavities. This last communicating cleft lies between the outer nasal process and the upper maxillary process of the first gill-arch. All the abnormal clefts of the face are explained by nonclosure of one or more of these primary clefts at the proper time. The defect may be superficial or may involve the maxillary and nasal bones and even the palatals. In some cases the amniotic bands which caused the clefts have been seen after birth. In many it is probable that the band had atrophied and disappeared in part at an early period, so that the cleft had a chance to close partly. A line like a scar is often seen continuing the direction of a cleft. Double-sided fissure of the face is more common than single; sometimes, from lack of frontal bones, a facial fissure will extend up into the skull.

Fissure or defect in development of the lower jaw is much less common than the above; and when it exists there is usually, in addition, a considerable defect in the mouth and the neighboring structures. The ears are set closer together and toward the under part of the head, when the lower jaw is considerably defective or absent (Fig. 148). Agnathus or lack of lower jaw is rare in man, but common in lambs. Abnormal openings from the outside into the trachea or esophagus or between these tubes are very uncommon.

Nonclosure of the clefts between the gill-arches may result in branchial clefts, branchial fistulæ, or branchial cysts, according to the extent and position of the imperfect closure. The persistent cleft is more often the second or third, and the outer opening is commonly a few centimeters above the sternum and at the inner border of the sternomastoid.

Thoracocœloschisis.—Fissure of the thorax alone is rare in man, but more often exists in connection with fissure of the abdomen. Like the latter, it may be caused by a fold of the yolk-sac getting between the edges of the developing thoracic wall, hypertrophy or displacement of some internal organ, or other interference with closure of the two sides

of the sternum. Up to the end of the second week, the heart projects above the ventral plates which, by their union, are to form the anterior body-wall; therefore any hindrance to the closure of these plates in the median line is likely to allow the heart to be displaced forward, so that finally it lies wholly or in part outside of the chest-cavity. The region of the navel, normally the last to close, is a favorite seat of fissure. Persistent cysts of the urachus, hypertrophy of abdominal viscera, or other accident which places a body between the uniting halves of the abdominal wall, may cause the defect in the median line. Marked retroflexion of the embryonic body may force the abdominal organs between the edges of the ventral cleft, thus inhibiting its closure.

Fissure of the lower abdomen and fissure of the pubes are probably often or always caused by bursting of the allantois, which acts as the primitive bladder. Some cause which closes the normal opening of the allantois at the umbilical end of the urachus, after the primitive closing of the opening into the cloaca at the second week, would compel the urine to distend the allantoic sac enough to burst it. Then the fluid would pass directly into the amniotic cavity through the rent, and thus prevent union of the bladder and pubic articulation in front. This fissure of the bladder may extend to the urethra or involve only that canal, as in the condition known as epispadias. This defect in the dorsum of the penis is a rare condition, occurring only once to 150 cases of hypospadias, or defect of the lower side of the penis and urethra. Up to about the fifth week, the gut and urinary passages open into the allantois and find outlet by way of the urachus and umbilicus.



FIG. 148.—Agnathus ectromelus apus.

If the re-opening of the cloaca is tardy, the allantois fills and distends as the urachal opening closes; and this distention of the allantois may prevent union of Mueller's ducts, and thus cause double uterus or vagina.

Hermaphroditism.—Until the etiology of sex is determined, it will be impossible to make a clear and full explanation of the phenomena of hermaphroditism, which cannot be said to consist merely in anomalies in closure of the urogenital cleft. In the early embryo, sex is apparently neuter. Locally, hermaphroditism consists in persistence in one sex of some of the structures belonging to the other sex, but which are normally present in an early period of the embryonic existence. The external genitals are formed by union in different ways of the margins of the urogenital cleft and cloaca. In the male the union is complete, while in the female there is left a cleft which becomes the vulva and opens into the vagina. Internally the genital organs are formed in the male from the Wolffian body and duct, and in the female from the Muellerian duct. In either sex normally the unused duct atrophies, but in internal hermaphroditism more or less development of the other ducts takes place. Where there is an anomalous development of the external genitals, there is apt to be also an anomalous development of the internal genitals. Besides these factors, there are usually general bodily and mental characteristics of the simulated sex present in the individual. True hermaphroditism, involving the production in the same person of both ova and spermatozoa, has never yet been authentically recorded, although there have been instances of the presence of organs histologically like ovaries and testes.

Klebs classifies true hermaphrodites (so called) and pseudohermaphrodites.

True Hermaphroditism.—These cases have both ovaries and testes, and take their gender from the organs which functionate. They may be *bilateral*, with an ovary and a testis on each side; *unilateral*, with an ovary on one side and a testis on the other; *lateral*, with both an ovary and a testis on one side and no sexual gland at all on the other. In all these cases, there will also be an amphimorphous condition of the external genitals. Very few cases are authentic.

Pseudohermaphroditism.—In these cases the sexual glands will be either ovaries or testes, but there will be an amphimorphous condition of the external and internal genitals. There are male or female pseudohermaphrodites, according to the sex of the glands. Autopsy is sometimes necessary to verify the sex, which, in the large majority of instances, is masculine. The degrees of male pseudohermaphroditism run from the mere enlargement of the prostatic vesicle, through the cases of rudimentary penis with more or less hypospadias, to those with a complete uterus masculinus, tubes, vagina, and urogenital cleft. Female pseudohermaphroditism is very rare and requires very strong evidence to be credited. Such individuals have a rudimentary vagina, and sometimes a uterus, a hypertrophied clitoris which more or less resembles a hypospadiac penis. The ovaries are sometimes prolapsed into the labia, making the last look like a scrotum.

In cases of even slight pseudohermaphroditism, where the generative organs only slightly resemble those of the opposite sex, there are usually appearances of the other sex in other parts of the body or even in the mental and moral nature. Thus a man with marked hypospadias, rudiments of a vulva, and a small penis is very apt to have something of the female type to his shoulders, breasts, or hips, to have scanty beard or the female type of pubic hair.

Craniorhachischisis.—The neural canal runs the whole length of the dorsum of the embryo, and closes at different times in different parts of its course by a folding-over of the posterior vertebral and cranial plates. Incompleteness of this normal closure in any or all parts results in the deformity in question. Dropsy of the cerebrospinal tissues, membranes, or central canal may be one cause of such nonclosure. Such a dropsical condition is a very common disease of the fetus, and is due to disturbances in circulation, perhaps resulting from cardiac or renal disease in the embryo, and often associated with edema of the whole body. Such cerebrospinal dropsy may cause hydrocephalus with stretching of the cranium, atrophy of the contained brain or more or less defectiveness of the bony covering, with consequent deformity of the brain, depending upon the time when the hydrostatic pressure is first exercised.

Hydrocephalus of the congenital kind is almost always internal, involving the ventricles. The internal pressure may cause atrophy of the cerebral tissue and enlargement and thinning of the cranial bones, with increased number and size of the fontanels. On account of hindrance to development of the forebrain, from which the primitive optic processes start, hydrocephalus is often associated with defective development of the eyes. When there is a pressure from a collection of fluid in the ventricles, and the bony vault is partly lacking, there results a protrusion of part of the cranial contents which is known as encephalocele, hydrencephalocele, meningocele, or hernia cerebri. In these cases, the cranial contents are partly included within a fluctuating tumor having its base in the cranium. The great majority of such protrusions are in the occipital region. If the destructive effect of the intracranial pressure is sufficient and acts at the proper time, there may be complete absence of the bony covering of the brain and cord, with more or less complete loss of these structures.

By no means all the forms of craniorhachischisis can be explained by pressure of dropsical fluid within the craniovertebral cavity. Those forms particularly in which there is a greater or less retroflexion of the fetal body, and also those in which a considerable mass of brain-tissue lies uncovered by bone, can hardly be explained in this way. For the exencephali at least, and probably also for a large number of the anencephali, the cause is doubtless an adhesion of some part of the amnion to some part of the dorsum of the embryo, and a consequent distortion of the coverings of the brain and cord. Circulatory disturbances, or even infectious amniotitis, not infrequently exist, especially at early embryonic periods. These disorders may easily cause adhesions of the overlying amnion to some part of the ectodermal layer of the embryo. A common place for such adhesions would naturally be where the amnion lies close to the embryo, such as the dorsum of the head and cervical region, where the cephalic end of the embryo dips down into the ovum. This is also the earliest portion of the amnion to form, and this portion of the embryo is the most often affected with defective closure of the neural canal. The adhesion for a time of a part of the amnion would destroy certain cells, while the neighboring cells would go on in their work of developing the surrounding parts, so that a defect would result which might cause grave malformation of the dorsum of the fetus and retroflexion of the fetal body. The rest of the body would grow, while the cells affected by the adherent amnion would for a time remain stationary; and at the same time, enough cells of the embryo would be destroyed to

cause a defect in the covering of the brain and cord or of these structures themselves. Traces of such adherent bands are sometimes found at birth (Fig. 149).

Craniorhachischisis may be divided into three genera: *Anencephalia*, in which there is more or less complete absence of brain; *Exencephalia*, in



FIG. 149.—Anencephalus showing persistent adherent amniotic band.

which there is considerable brain-tissue placed wholly or partly outside of the cranial cavity; and *Spina bifida*, in which the chief defect is in the dorsal plates of the vertebræ. With the first two, the third often co-exists.

Anencephalia.—Two species may be distinguished: the first with retroflexion of the fetal body (Fig. 150), which is usually accompanied with



FIG. 150.—Anencephalus.

more or less *spina bifida*; and the second without retroflexion, where the vertebral canal is usually open only in the upper cervical region. *Anencephalus*, which is the most frequent form of monstrosity, is characterized by absence or the merest traces of brain and by extensive defect in the bony

vault of the cranium. The squamous portions of the cranial bones are so rudimentary that the head looks as if removed just above the forehead and ears. The base of the skull, deprived of the pressure of the brain above it, usually becomes concave and therefore foreshortened. These monsters seldom live more than a few minutes and never more than a few days, probably because they lack the influence of a brain to direct the vital processes. On the other hand, the bodies are often remarkably well developed and nourished, sometimes enough to cause dystocia on account of the size. The cranial and spinal nerves are present. Other malformations, especially those which seem to be due to the influence of amniotic bands and adhesions, such as harelip, club-foot, amputated limbs, and the



FIG. 151.—Hyperencephalus.

like, frequently co-exist. The sex is female in more than three-fourths of the cases. In the retroflexed species, on account of the lordosis and tilting-back of the head, the neck-furrow is obliterated and the head seems to be set low between the shoulders. The lordosis is greatest in the cervical region, so that here is left a deep cavity in the vertebral canal. Those cases which have rudiments of brain-tissue upon the base of the skull are called *pseudencephali*. The base of the skull and vertebral canal (if open) are covered with membrane, around which is a fringe of hair in a horseshoe form. Since the supra-orbital ridges are the topmost parts of the skull, they make the eyes stick out and give the frog or owl appearance so often described.

Exencephalia.—In this genus there is a defect in the cranium, through which the brain or its membranes protrude, lying outside the cranial cavity to a greater or less degree. The genus is divided into species, according to the place of exit of the encephalocele.

Proencephalus has a defect in the anterior part of the skull, the orbit, ethmoid, frontonasal region, or frontal bone. The hernial protrusion is usually largely meningeal, containing little cerebral tissue. The tumor may present in the orbit, in the nasal cavity, in the pharynx, alongside the nose, or in the forehead. The form is rare.

Hyperencephalus (Fig. 151) is that species in which the bony defect is in the vertex, usually involving the frontals and parietals. It varies in extent from a small meningeal tumor at the top of the head to one which contains



FIG. 152.—Notencephalus.

almost the whole brain, in consequence of which the cranial bones are rudimentary. Podencephalus is the term used to designate these extensive forms.

Notencephalus is characterized by a defect in the occiput (Fig. 152), through which the cerebral tumor protrudes, to hang down the back of the neck like a chignon. Depending chiefly on the size of the opening in the bone, the tumor may be large or small, containing little or most of the brain. In the latter case, the rest of the cranial bones will lie flat against the base and be rudimentary, because not stretched out by the growth of a normal brain within them. If the tumor is small and can be protected from external injury, the child may live indefinitely, even to adult life.

Infiencephalus is characterized by a defect in the middle of the squamous portion of the occiput, accompanied by a fetal retroflexion and cervical spina

bifida so situated that the brain lies upon the bodies of the cervical vertebræ, but is covered by the bones of the cranial vault. The margins of the occipital defect articulate more or less completely with the margins of the spina bifida, thus closing in the brain. If this articulation is complete, there will be no protrusion of the brain-tissue at all; otherwise there may be an encephalocele in addition. Iniencephalus is relatively rare; less than thirty cases have been reported.

Exencephalus proprius (Fig. 153) has the fetal retroflexion, cervical spina bifida, and tilting backward of the head, as in iniencephalus; but the bones of the cranium are rudimentary, so that the brain lies exposed upon the base of the skull or the vertebræ. Males predominate, and the species is rare.

Spina Bifida.—This malformation is very common, existing both in connection with cranioschisis and alone. The vertebral laminæ do not unite for



FIG. 153.—*Exencephalus proprius*.

part or all the course of the column, and the transverse processes lie flattened out. There may be a membrane covering the open spinal canal, under which are spread out the flattened fibers of the cord; or, if the opening is circumscribed, the meninges may protrude between the divided bones in the form of a sac, sometimes covered with skin and sometimes with a membrane derived from the outer side of the dura. The inner lining of the sac is the inner surface of the spinal membranes, the contents are cerebrospinal fluid, and nervous filaments run along the walls of the cyst. The most common seats of spina bifida are the lumbar and cervical regions, parts of the canal which normally close last.

Cyclopia.—Cyclopia or synopsia is an example of defective development of the anterior parts of the brain and of the optic buds. In microcephalus, there is a defective development of the whole brain. The eyes develop from budding forward of projections of the forebrain. When from causes more

or less obscure the forebrain is defectively developed, the eye-stalks may start close together or even be fused; so that when the optic vesicle reaches its full length, only one eye or a fused eye will be formed. The optic vesicles are begun very early, before the bones or before the union of the parts making up the face; so that, if the cyclopic eye already occupies the center of the face, the nasal plates are forced to grow elsewhere, usually above the eye. For this reason, we commonly have a rudimentary and often grotesque proboscis jutting out from the middle of the forehead above the eye. The internal bones and cavities of the nasal apparatus are lacking. Cyclopia runs through all degrees, from mere narrowing of the space between the eyes to a single optic globe or orbit or even total absence of the eye. The brain is always more or less defective in the anterior portions. The monsters are not viable.

There are certain irregular actions of amniotic bands and adhesions which produce various forms of malformation. In the so-called amputations of limbs, it is doubtful if the umbilical cord or amniotic band actually cuts off limbs already formed; but it seems more than likely that pressure of such bands, and also adhesions of parts of the amnion with the ends of limb-buds, may prevent further growth, so that such a limb or digit in later life appears as if cut off. Bands may bind digits together so that they appear webbed, or even, at an early stage, extensive contraction or adhesions of the amnion may cause the anlagen of both legs to fuse and produce *Sirenomelus* or sympodiac monsters. The different forms of *Ectromelus* may have a similar etiology.

The conditions of talipes, atresia, local and general hypertrophy, local and general dwarfism, and various other malformations, as well as the hemiterata and heterotaxis, are considered in other parts of this work.

SPECIAL PATHOLOGY.

THE BLOOD AND THE BLOOD-MAKING ORGANS.

METHODS OF BLOOD-EXAMINATION.

It seems best to give a brief account of the principal methods and instruments by which our present knowledge of diseased states of the blood

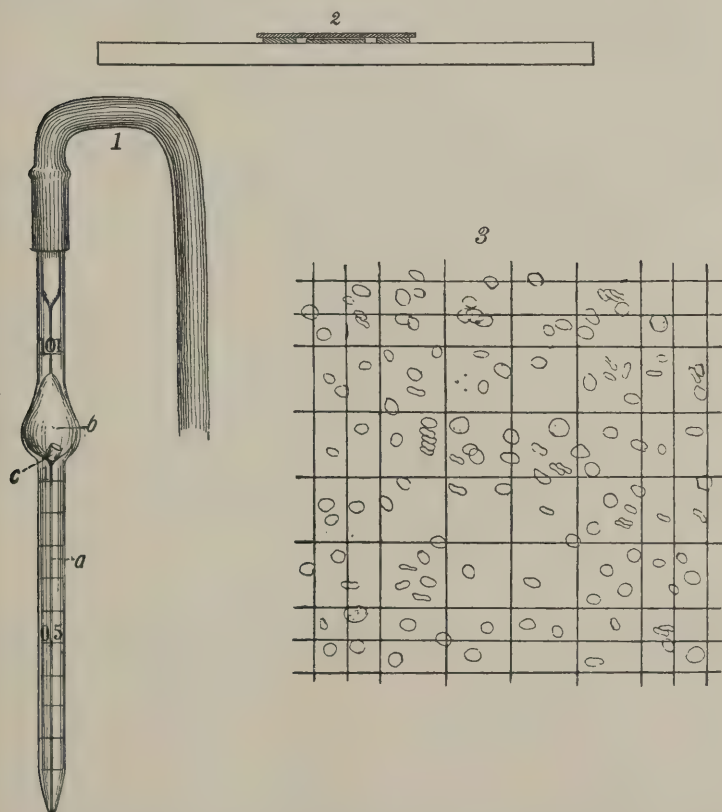


FIG. 154.—Thoma-Zeiss blood-counting apparatus. 1. Mixing apparatus: *a*, Capillary tube in which the blood is taken; *b*, chamber for mixing the blood with the diluting solution; *c*, glass ball to aid in mixing the blood with the diluting solution. 2. Cross-section of the chamber in which the blood is counted. 3. Section of the field on which the blood is counted, showing thirty-six squares.

and blood-making organs has been built up. These are : Examination of the fresh blood (uncoagulated); enumeration of the red corpuscles and of the leukocytes; hemoglobin-estimation; examination of stained cover-glass

preparations of the blood, lymph, and fresh bone-marrow; bacteriologic examination of cultures from the blood; examination of the serum (serum diagnosis).

Other methods of examination, such as those dealing with the alkalinity, isotonic coefficient, rapidity of coagulation, freezing-point, molecular concentration, hemolytic and bacteriolytic properties, and chemical composition of the blood, do not fall within the scope of this article.

Examination of fresh blood, which is especially valuable in the search for parasites, such as the malarial organism, the spirochete of relapsing fever, and the *Filaria sanguinis hominis*, is performed as follows:

Carefully clean and warm a slide and cover-glass; puncture the lobe of the patient's ear with a bayonet-pointed surgical needle; touch the *summit* of the exuding blood-drop with the center of the cover-glass (held with pincers) and immediately drop it upon the warmed slide. The blood should spread so evenly that rouleaux are not formed and the red cells do not overlies one another. If it is desired to keep the specimen fresh for more than twenty minutes, the margins of the cover-glass may be sealed to the slide with vaselin or cedar oil.

Counting Blood-corpuscles.—The instrument of Thoma-Zeiss (Fig. 154) is the best. It consists of a pipet (*a*), in the bulb of which (*b*) a given amount of the blood is mixed with a neutral diluting solution 100 or 200 times its bulk,¹ by sucking blood up to the mark "0.5" on the tube and then sucking the diluting solution after it until the bulb (*b*) is full of the mixture. A drop of this mixture is then blown out upon the disk (Fig. 154), the size of the drop being calculated so that, when the "roof" of the counting-chamber is let down over it, the drop covers the disk without spilling over into the "mote." On the surface of the disk, which is ruled in squares of $\frac{1}{400}$ of a square millimeter, the corpuscles settle evenly and can be counted. At least 200 small squares should be counted. The average number of corpuscles in 1 square multiplied by 800,000 gives the number in 1 c.mm. of blood, if the dilution be 1:200.

For counting red corpuscles a convenient diluting solution is that of Gowers, made as follows:

Sodium sulphate,	gr. ciiij;
Dilute acetic acid,	ʒj;
Water,	ʒiv.

Or Torson's fluid, which also stains the white corpuscles. This consists of

Methyl violet,	0.025 gm.;
Glycerin,	30 c.c.;
Distilled water,	80 c.c.

To this is added

Sodium chlorid,	1 gm.;
Sodium sulphate,	8 gm.;
Distilled water,	80 c.c.

The solution is then filtered.

The white corpuscles appear on the ruled surface of the disk (*a*), when Gowers's fluid is used, not much whiter than the red ones, but much

¹ Ten or twenty times its bulk when the leukocytes only are to be counted.

more highly refractile. The number present in a dilution of 1:200 is so small that considerable errors result from calculations based on it. It is better to dilute only 1:20 when we desire to count the leukocytes, using a large-bore pipet made by Zeiss for the purpose and a $\frac{1}{2}$ per cent. aqueous solution of glacial acetic acid. This renders the red cells invisible and leaves only the leukocytes in the field. The whole number present on the ruled surface should be counted in each of at least two drops. The total number found in two drops multiplied by 100 gives the number per c.mm. of blood.

In practised hands the error is not over 5 per cent. There are many important details in the correct technic of blood-counting, for which we

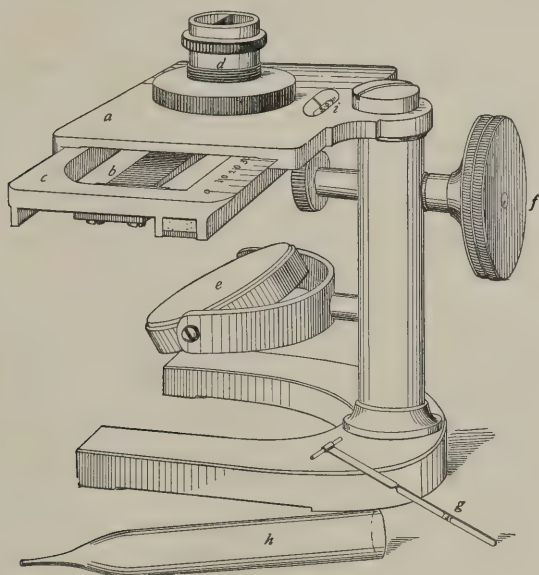


FIG. 155.—Von Fleischl's hemoglobinometer: *a*, stand; *b*, narrow wedge-shaped piece of colored glass fitted into a frame (*c*), which passes under the chamber; *d*, hollow metal cylinder, divided into two compartments, which holds the blood and water; *e*, white plate from which the light is reflected through the chamber; *f*, screw by which the frame containing the colored glass is moved; *g*, capillary tube to collect the blood; *h*, pipet for adding the water; *i*, opening through which may be seen the scale indicating percentage of hemoglobin.

have here no space; they may be studied in special treatises on the subject.

Hemoglobin Estimation.—Von Fleischl's hemoglobinometer (Fig. 155), which is in general use, has a very wide range of error. The principle of the instrument is the endeavor directly to compare the tint of a measured amount of blood with the tint of various portions of a wedge of red glass, the color of which shades gradually from deep red at one end to clear glass at the other. In most hands an error of 10 to 20 per cent. is inevitable. Gowers's hemoglobinometer depends also on the principle of color comparison, but instead of a wedge a tube containing colored gelatin is used. The error is not so large as with Fleischl's instrument, but the color of the wedge fades a little in time, making the reading higher than it should be.

Examination of Stained Specimens.—A drop of blood taken on the surface of a clean cover-glass, as above directed, is covered with a second cover-glass in such a way that their corners do *not* coincide. If both are perfectly clean and are held with forceps, the blood instantly spreads so as to make a layer one cell thick. As soon as the blood stops spreading, the upper cover-glass is rapidly slid off without raising or tilting it, and an even layer is left on each glass.

After drying in the air, such specimens are best fixed by heating in an oven to 120°–140° C. or by passing them from fifteen to twenty times through the tip of a Bunsen-burner flame. If the latter method is used, we can only determine by practice how rapidly the cover-glass should move through the flame. Overheated specimens stain too faintly; underheated ones stain too intensely. The happy mean can be learned only by experience.

By far the best stain for such specimens is that known as Ehrlich's "triacid" mixture. The formula is as follows:

Sat. aq. sol. orange G., ¹	120–135 c.c. ;
Sat. aq. sol. acid fuchsin,	80–165 c.c. ;
Sat. aq. sol. methyl green,	125 c.c. ;
Glycerin,	100 c.c. ;
Absolute alcohol,	200 c.c. ;
Water,	300 c.c.

A single drop of this mixture is spread with a glass rod on the specimen and left there at least three minutes, or as much longer as is convenient. It is impossible to overstain a properly prepared and fixed specimen. The stain is then washed off with water, the specimen dried with blotting-paper and mounted in balsam. Hewes has improved upon this stain by counter-staining the covers for one to three seconds with Löffler's blue. The nuclei are much better seen in this way. The appearances of a specimen so prepared will be described later.

Examination of the fresh marrow is best made by smearing as thin a layer as possible between two cover-glasses, which are then fixed and stained as above directed.

Pieces should be hardened in Zenker's fluid and embedded and cut in the ordinary way. Eosin and hematoxylin form the best stain for such preparations.

Bacteriologic Examination.—Render the skin over the surface of the bend of the patient's arm reasonably aseptic. Compress the arm above the elbow so as to make the veins stand out. Plunge the needle of a sterile hypodermic syringe into the largest vein visible and withdraw a syringe-ful of blood. This blood can then be poured down over the slant of a blood-serum or agar-agar tube or mixed with softened agar-agar, according to the nature of the organism looked for. In cases of ulcerative endocarditis, pyemia, pneumonia, and gonorrhea, micro-organisms are not infrequently obtained in this way.

Serum Diagnosis.—(See pages 237 and 270.)

¹ Colors are best obtained of G. Grüber & Co., Leipzig.

DISEASES OF THE BLOOD AND THE BLOOD-MAKING
ORGANS.

INTRODUCTION.

The limits of this subject are becoming constantly more difficult to define. Strictly speaking, there are no diseases which we know to affect primarily the blood, except possibly malaria and a few other parasitic diseases. All diseases probably affect the blood to a greater or less degree, and it is arbitrary how many we include under diseases of the blood itself.

There seems to be almost as much reason for classing diabetes and other so-called constitutional diseases with blood diseases as there is for including chlorosis. The blood changes are results of deeper causes equally in the one case as in the other. Every change which we describe in our accounts of diseased blood is a symptom which may result from any of various causes. In some cases, as in secondary anemia, we are aware of the fact that the blood changes are only symptomatic of some underlying malady, like cancer or cirrhosis of the liver. In chlorosis and pernicious anemia, there is but little likelihood that the blood changes are any less "secondary," since they are identical with conditions of the blood due to well-known causes, such as intestinal parasites or traumatic hemorrhage. In all probability the blood of pernicious anemia and chlorosis simply reflects the action of deeper and more primary causes, the nature of which is at present not understood. As we now speak of "diseases of the blood," so we should have to speak of "diseases of the urine," and probably to include therein the changes which the urine undergoes in a great variety of diseases, were it not that we have in this case definite organs—the kidney, the bladder, etc.—which we can examine in connection with urinary changes, and thus correlate certain of the urinary disorders with disease in one or another of these organs. As regards the blood, we are not so far advanced. The reproduction of blood-tissue probably occurs in a great many different places, no one of which is set aside for that function alone—like the heart for pumping, or the bladder for storage.

All diseases affecting the various localities in which blood-cells breed cannot be classed as diseases of the blood or blood-making organs. Thus, although we ordinarily speak of the bone-marrow and the lymphatic apparatus (adenoid tissue wherever found) as blood-making organs, we should not think of classing osteomyelitis or syphilitic adenitis under blood diseases.

If, on the other hand, we drop the "blood-making organs" altogether, and class under "diseases of the blood" all such and only such as show relatively striking changes in the circulating blood-tissue itself, we should be bound to exclude Hodgkin's disease and the hemorrhagic diseases (scurvy, purpura, hemophilia, etc.), in which no marked alterations of the blood are, as far as we know at present, constant; and furthermore, to include diabetes, Asiatic cholera, and the bubonic plague, in all of which the blood shows as great aberrations from normal as in chlorosis.

It is best, therefore, to admit that we have no good or sufficient reason either for our inclusions or for our exclusions, in making out our list of diseases of the blood. Under this heading are classed for convenience a number of quite heterogeneous pathologic conditions which do not easily find a better

place in other groups and which custom and outgrown theories have placed together. Having no better positive classification to propose, we shall in this article include the traditional list, viz.: Secondary anemia, chlorosis, pernicious anemia, leukocytosis, leukemia, Hodgkin's disease, hemophilia, scurvy, purpura.

In order to make intelligible what is to be said in the next section as to pathologic conditions of the blood, some general description of the normal morphology of the blood must be attempted. We usually speak of blood as made up of red corpuscles or erythrocytes, white corpuscles or leukocytes, blood-plates, and plasma, in which the above elements move or are carried.

Red Corpuscles.—In the circulating blood of healthy adults, the so-called red corpuscles are recognized easily as circular, slightly biconcave disks from 6μ to 9μ in diameter and about 1μ in thickness. In infancy, larger and smaller forms are found, even in health; but in the adult, anything beyond these limits is considered pathologic. Seen by transmitted light, the "red" corpuscle is of a very pale, slightly greenish-yellow color. No distinct nucleus is made out, although Arnold and others adduce evidence that in the mature cell there are appearances which might correspond to the *remains* of the nucleus which is present in every red corpuscle at an earlier stage of its development. In early embryonic life, all red blood-cells are nucleated and are mostly of much larger size than those seen in postembryonic life. Later in embryonic life, they begin to lose their nuclei, which break up and fade out; and such nucleated cells as are still seen are much smaller, in the main, than those of embryonic life. Finally, at birth and thereafter, there are no nucleated cells in the circulating blood; but in the bone-marrow the smaller nucleated forms persist, and are especially plentiful there after hemorrhage, in the course of acute infectious diseases, or in anemic conditions when blood repair is called for. The bearing of these facts on diseased conditions of the blood will be seen later.

Although it is generally agreed at present that red blood-corpuscles are developed from nucleated corpuscles or erythroblasts—which are formed in embryonic life in the liver, spleen, and elsewhere, and in adult life in the bone-marrow alone—their *primary* origin is still a matter of doubt. The weight of opinion seems to support the view that red cells are not developed from leukocytes nor from an ancestor common to both red and white corpuscles, but have an independent origin, probably from the angioblastic cells of the mesoblast.

In healthy adults the number of red corpuscles is about 5,500,000 per cubic millimeter. They stain well with acid anilin dyes (eosin, fuchsin, etc.), and comparatively feebly with basic dyes. In certain pathologic conditions, their affinities become neutralized or reversed.

Leukocytes.—Among other tissues of the body, "red" corpuscles can be distinguished by their hemoglobin, which gives them a peculiar color and staining reaction;¹ and even when they are nucleated they can be distinguished from other tissues in this way.

For leukocytes, on the other hand, we have no such distinguishing mark. We cannot simply agree to call all colorless cells found in circulating blood by the name of leukocytes and exclude all others; for, aside from the well-known fact of the "emigration" of leukocytes from the vessels and into

¹ It is true that we have no absolutely unique and specific staining reaction for hemoglobin, but there are very few conditions in which other cells stain like it.

various tissues, we find cells in all respects similar to leukocytes which reside permanently or almost permanently in various other places. It is generally agreed, for example, that the small mononuclear cells which are so plentiful in fluid lymph and chyle and in lymphatic glands are identical with the smallest forms of blood-leukocytes, and that the majority of the cells in ordinary pus are identical with the larger forms of blood-leukocytes. It is further shown by recent English researches that the large body-cavities contain large numbers of free cells, many of which are in all respects similar to the coarse granular leukocytes of circulating blood, and other cells which are occasionally seen in the blood. That the cells which make up the germ-centers of lymphoid tissue and the bulk of those found in normal bone-marrow (exclusive of fat) may also be found in the blood is likewise well established.

The wandering cells of the alimentary canal, of the diaphragm, and many of those found in connective tissue are in all probability to be classed as leukocytes more or less altered by the conditions of their environment.

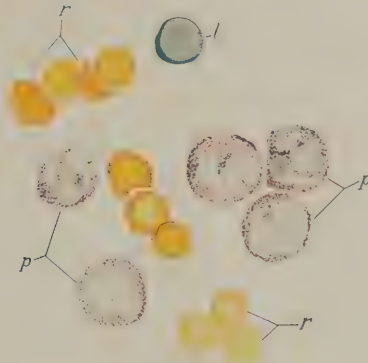


FIG. 156.—Leukocytosis: *l*, lymphocytes; *p*, *p*, polynuclear neutrophiles; *r*, *r*, red cells. (Cover-glass film from a case of pneumonia, stained with Ehrlich's "triacid" and drawn with camera lucida.)

This includes the mast-cells of connective-tissue structures. As to Unna's "plasma-cells," I am not prepared to speak confidently; but they also are very possibly to be included under the same heading. Cells very closely resembling them may be seen in the blood of lymphatic leukemia. The varieties included in this list are not more different from each other than from the different types of colorless corpuscles always present in normal circulating blood. If it be objected that the term "leukocyte" is thus made a sort of "omnibus" into which is packed a heterogeneous mass of cells of all types, the answer is, first, that the leukocytes of circulating blood are equally heterogeneous; and secondly, that transitional forms between each of the varieties can be found.

The differences between them are probably due to (*a*) differences in the ages of the different cells, and (*b*) to differences in environment (marrow, celomic spaces, blood, connective tissue) into which they wander.

Representatives of all these types are found in the marrow, where no doubt many of them arise; and here, as in the spleen, body-cavities, and elsewhere, we find the giant cells or macrophages, which differ from the

leukocytes of circulating blood only in the size to which their free quarters allow them to develop. They are too large, many of them, to pass the capillaries.

Our knowledge of these various forms would never have been possible without the use of the combinations of anilin staining methods introduced by Ehrlich. With the aid of his staining methods we recognize in normal blood the following types of leukocytes:¹

Lymphocytes.—Spheric cells from 5 to 10 μ in diameter, mostly filled by a spheric nucleus,² nonameboid, indistinguishable from the small elements of lymphoid tissue and lymphoid infiltrations or from the lymph- and chyle-corpuscles. The nucleus stains intensely with simple basic stains. With Ehrlich's triacid mixture the nucleus is often pale and shows a delicate chromatin network. The protoplasm may not stain at all with acid dyes. It can be stained irregularly with basic dyes, the extreme periphery showing a greater affinity for basic dyes, while the portion in contact with the nucleus shows a preference for acid stains. With double or triple stains, it often shows its affinity for both kinds of dyes by taking up a mixture of two or more dyes. Thus, with eosin and methylene-blue, it may stain purple; with Ehrlich's triacid mixture, gray. Basic stains bring out coarse blue granules in the protoplasm of some of the lymphocytes.

Other cells are like those just described, but considerably larger and with a relatively larger amount of protoplasm. Such cells may be from 10 to 17 μ in diameter. In the large forms the nucleus stains less well and is not infrequently more or less indented or bent, with its borders ill-defined.

In the blood of many healthy persons there may be seen every intermediate size between this variety and that first described, so that the distinction appears entirely arbitrary. In other cases, all cells of this general type are either under 8 μ or over 13 μ diameter, with none at all of the sizes intermediate between these measurements. In such cases, either the small type or the large may be the more numerous. As a rule, the small forms are four or five times more numerous than the large. Together, the large and the small lymphocytes make up from 25 to 45 per cent. of the colorless corpuscles of normal blood. Their number is considerably increased after meals and by various other influences. The larger forms are somewhat ameboid and phagocytic. In the protoplasm of the larger forms, especially near the periphery, fine basophilic granules may be seen.

Polymorphonuclear Neutrophiles.—Diameter in cover-glass specimens ordinarily from 11 to 15 μ , averaging 13.5 μ ; nucleus sausage-shaped, occupying a relatively small space in the cell-body and taking on a great variety of contorted appearances, whence its name. In many instances the nucleus appears to have divided into two or more segments, but good staining usually shows that the apparent divisions are bridged by constricted portions which join the large nuclear fragments with one another. This nucleus stains more deeply and shows less structure than that of any other variety of leukocyte. The protoplasm stains diffusely with aqueous solutions of acid dyes; very faintly, if at all, with basic dyes. Alcoholic solutions of acid dyes (eosin, acid fuchsin) bring out a fine pinkish granulation in the protoplasm. These granules are much more distinctly brought out by differential acid stains,

¹ The confused nature of the terminology here followed is apparent to the writer. But, in the absence of a better basis of classification, the traditional one is adhered to.

² Rarely indented or divided.

such as Ehrlich's triacid. They have been called "neutrophilic" because neither simple acid stains, like eosin, nor simple basic stains, like methylene-blue, bring them out clearly. There are probably no genuinely *neutral* stains in use. With Ehrlich's triacid mixture, these granules stand out as purple or violet dots against a colorless or faintly pinkish background. They are seen over and around, but not *in*, the nucleus.

These cells are actively ameboid and phagocytic, although they do not have by any means a monopoly of the function of phagocytosis, which is also exercised by the large lymphocytes. At rest outside the body and in the bone-marrow, the nucleus assumes a spheric shape. Its twisted and irregular shape is probably due partly to its ameboid movement, partly to growing old.

Between this cell and the lymphocytes we see scarcely any transitional forms in normal circulating blood. But in some cases of leukemia many intermediate forms are seen, as also in smear preparations from the normal bone-marrow.

Polymorphonuclear neutrophiles make up from 60 to 70 per cent. of the leukocytes of normal circulating blood. In the celomic spaces they are much less numerous, while the lymphocytes and eosinophiles are much more plentiful there than in the blood. The great majority of cells in ordinary pus are neutrophiles. In the blood of lower animals there are no neutrophilic cells.

Eosinophiles.—From 1 to 4 per cent. of the white corpuscles of normal blood show, when stained with eosin, a number of brilliantly colored pink granules in their protoplasm. These granules are much larger and more highly refractive than the neutrophilic granules, and are nearly of uniform size. They are spheric or more rarely oval, and no cell-body can be made out between them by any method of staining. They are grouped loosely around or at the side of the nucleus, which seems attached to them rather than embedded in them. The nucleus stains feebly with basic dyes, and it is difficult to make out a structure in it. Frequently it is divided into two or more parts, between which no connection can be made out. The cell, as a whole, is slightly smaller than the neutrophile and much more irregularly shaped. It is the most actively ameboid leukocyte. In normal blood eosinophiles are few; but in the celomic spaces, in the bone-marrow, and in connective tissue, they are much more abundant. Transition forms between them and the neutrophiles do not occur in normal blood.

Mast-cells.—In normal blood these cells constitute about $\frac{1}{2}$ per cent. of the leukocytes. Their nucleus is irregularly trilobed and embedded in a protoplasm which with Ehrlich's triacid remains unstained, but with basic stains shows irregular clumps of dark blue. In myelogenous leukemia they are frequent.

This completes the list of varieties of leukocytes in the blood-vessels of normal adults. The absence or great rarity of transitional forms between any of the three varieties just described makes it very unlikely that such transitions take place in the peripheral circulation. On the other hand, the fact that in leukemic blood and in the normal marrow may be found an abundance of transition forms of all kinds makes it unlikely that the different varieties seen in normal circulating blood are ultimately of different origin. In the peripheral blood we get only a short phase of the development of leukocytes, viz., from the small to the large lymphocyte. Then there is a gap

between the large lymphocyte and the polymorphonuclear neutrophile, the intermediate forms being found chiefly in the marrow. Among such intermediate forms should be reckoned the *myelocyte*, to which reference will be made later. Possibly also the various types of *basophiles* (*vide infra*) are to be looked upon as normal phases of development of leukocytes in certain environments, under conditions furnished by the marrow, the celomic and connective-tissue spaces, but not by the blood. We need not assume that every leukocyte normally goes through all these stages. They may all start alike—*i. e.*, as lymphocytes—but be so affected by the conditions of their environment that some never get beyond the lymphocyte stage, while others develop into neutrophiles, basophiles, or eosinophiles, according to their surroundings. The blood receives from various sources a given number of cells in various stages of evolution. What are the laws which govern the number of each variety that shall be put in circulation and the manner of keeping the percentages fixed? We have no idea.

Blood-plates.—Besides the red disks and leukocytes, we find in normal blood a varying number of small, colorless, nonameboid elements about 2 or 3 μ in diameter and of various shapes, oval being the commonest. They often cohere in masses which have been compared to bunches of grapes. No nucleus can be made out. Their staining affinities are not constant; some have affinity for acid, others for basic dyes. There are many reasons for supposing that these so-called blood-plates or blood-platelets form a group which includes elements of various origins, fragments of red and of white corpuscles making up the bulk of their number. In health they number from 200,000 to 300,000 per c.mm.

Plasma.—Of the healthy plasma, there is little to be said that falls within the scope of this article. The variations in the amount of fluid in the vessels are considerable, even within physiologic limits, as the experiments of Oliver have shown. Influences acting as vasoconstrictive increase blood-pressure and force out into lymph-spaces more or less plasma, so that the number of corpuscles in a given volume is increased. When the blood-pressure is temporarily diminished, fluid from the surrounding tissues enters the vessels and dilutes the blood, so that the count of corpuscles per cubic millimeter is lessened. Such results must not be attributed to any change in the number of the corpuscles themselves, but only as local or temporary concentration or dilution.

ANEMIA.

As above stated, anemia is in all probability a symptom of some deeper trouble, toxic or other. It is perhaps best defined as "a condition of deterioration of the blood, with altered relations of the fluid and solid parts" (Stengel).

This deterioration is generally manifested by changes in the serum, which are probably at the root of the alterations seen in the corpuscles. In the corpuscles themselves the manifestations of anemia are: Diminution in corpuscle substance, either through loss of corpuscles or through loss of hemoglobin in each corpuscle; various degenerative changes (poikilocytosis, polychromatophilia, etc.); presence of unripe corpuscles (nucleated red cells, myelocytes, etc.).

So far we have referred wholly to qualitative changes in the serum and

corpuscles and quantitative changes in the latter. Of the existence of a true and continuous insufficiency in the total quantity of blood, we have no direct proof, though it is believed by some to occur, and many clinical facts suggest it.

The term "anemic" or "ischemic," as applied to an organ, usually refers to a pallor due either to diminished bulk of blood in the organ or diminished amount of coloring matter in the blood then present. The term is often applied to patients merely because of pallor of the skin; but this may be extreme without there being any discoverable changes in the amount or quality of the blood, and is probably then the result of vasomotor conditions.

We may distinguish acute anemia from loss of blood and chronic anemia due to qualitative changes in the blood. The distinction of "primary" and "secondary" anemia has already been briefly discussed on page 45. It is not probable that this distinction will stand the test of time; but it has still a certain usefulness if applied simply to group together, on the one hand, the cases of the cause of which we *are* aware (secondary anemias), and, on the other hand, those in which the important etiologic factor is unknown (primary anemias).

Bearing this in mind, we may classify anemias as "*primary*," including chlorosis and pernicious anemia, and "*secondary*" (due to carcinoma, hemorrhage, bad hygiene, etc.).

The terms "simple primary anemia," "splenic anemia," and "secondary pernicious anemia" should be discarded. "Simple primary anemia" refers either to skin pallor, from which the inference of anemia is made without corroborative blood examination, or else to secondary anemia from bad hygiene, rapid growth, or the like.

"Splenic anemia" refers to the association of anemia with enlargement of the spleen. But, as there is no one type of anemia which may not be attended by splenic tumor, there is no definite reason for using the term.

"Secondary pernicious anemia," a term used chiefly by German writers, refers to conditions more or less like those found in pernicious anemia, but associated with a definite cause, like carcinoma or nephritis. This blurs over an important distinction, since the blood changes in such cases are markedly different from those found in true pernicious anemia. In two or three cases, a single small cancerous nodule at the pylorus has been found at autopsy in cases of pernicious anemia, but there is no reason to believe that such a nodule can cause such an anemia.

PERNICIOUS ANEMIA.

A very large number of causes have been frequently mentioned in connection with the disease. Syphilis, malaria, child-bearing, hemorrhage (especially repeated small losses of blood), nervous shock, chronic gastrointestinal diseases, and many other affections have been supposed to cause the anemia. The evidence as presented goes to show that these influences have no effect unless perhaps as the straw that breaks the camel's back.

Any of these causes may be followed (a) by no considerable anemia, (b) by a characteristic secondary anemia (*vide* p. 472), (c) by pernicious anemia. But the number of cases in which pernicious anemia follows one of these affections is so small that the sequence is in all probability accidental.

The only genuine cause with which we are acquainted is the action of intestinal parasites, especially the *Bothriocephalus latus* and the *Ankylostoma duodenale*. The symptoms and signs, including the blood condition in cases caused by these parasites and cured by their expulsion, may be *identical* with those found in the so-called idiopathic and fatal cases. It is true that there are many cases in which these parasites inhabit the intestine without causing any anemia; but the frequent instances of cure immediately following the expulsion of the parasite make it probable that the parasite is the cause, in the same sense that lead is the cause of many colics and paralyses.

This fact, together with recent observations as to the method in which these parasites impoverish the blood, give us such notions as we have respecting the mode of production of nonparasitic cases. There is every reason to believe that the parasites do harm, not by the amount of blood which they actually suck into themselves and consume, but through the influence of some poison which they produce in the intestine and which is thence absorbed into the blood. If recently discharged proglottids of *Bothriocephalus* are fed to animals, an anemia is rapidly produced. This suggests that nonparasitic cases may be due to an auto-intoxication with products absorbed from the gastro-intestinal tract, under conditions of which we are ignorant.

Pernicious anemia is by no means an uncommon disease. The writer has had the opportunity of studying 110 cases within the last eight years. Its geographic distribution, apart from the parasitic forms, is probably in direct proportion to the activity of medical science in any given district.

Age and Sex.—Persons between forty and sixty years appear to be more subject to the disease than those above or below these limits. It is rare under the age of twenty; the author has seen two cases in patients past their seventieth year.

Among the author's cases there was a slight preponderance of males. Thus, of 110 cases, 57 were males and only 53 females. The older statistics, which include many cases following parturition, show about an equal number in each sex. The rarity of cases following parturition in the more recent statistics makes the correctness of the diagnosis in older accounts doubtful.

Morbid Anatomy.—The unknown poison which is now generally believed to be at the root of pernicious anemia expends itself chiefly in three ways: (*a*) On the blood; (*b*) on the spinal cord; (*c*) on the parenchyma of the heart, liver, and kidney, where extensive fatty degeneration is the striking change.

Secondary to these in all probability come: (*d*) Hemorrhages in various organs and from serous surfaces and mucous membranes; (*e*) compensatory changes in the bone-marrow; (*f*) deposits of iron-containing pigment, especially in the liver; (*g*) atrophy of the gastric mucosa (in some cases).

The Blood.—Gross Appearances.—The color of the drop, as it emerges from a puncture, varies a great deal. In most cases it is very pale and watery-looking, though not more so than is occasionally seen in severe cases of chlorosis or secondary anemia. But not infrequently the color of the blood in gross is as bright a red as normal blood, even when not over one-fifth of the normal number of corpuscles is present. The color in these cases is probably due to the high hemoglobin percentage present in all of the cases in which bright-red blood is seen in pernicious anemia.

The drop often looks streaked and particolored, as if the cells were separating themselves from the plasma; this appearance may be seen in any severe anemia.

As striking as the color of the drop is its great *fluidity*. The rapidity with which it slips off the ear or finger makes it difficult to manipulate it (embryonic blood shows a similar property).

Coagulation is very slow.

The *specific gravity* is usually much diminished—*e. g.*, to 1.025 (normal, 1.058).

Red Corpuscles.—*Quantitative Changes.*—Most cases show 1,000,000 to 2,000,000 cells per c.mm. when they first come under observation. The fall of the count to this point is often very rapid; while beyond this the fall, if it occurs, is slow. There are evidently conditions which tend to arrest the destructive process at this point. Thus, of the 110 cases mentioned, 79 showed between 1,000,000 and 2,000,000 corpuscles per c.mm. when first examined. The other 31 counts were below 1,000,000. Of these 31, 8 fell below 500,000 corpuscles per c.mm. before death. The lowest count in the series was 363,000. The lowest on record was reported by Quinke twenty years ago—143,000 per c.mm.

In some cases the corpuscles remain at practically the same figure until death; others progressively decline. Most frequently, however, one or more remissions occur, in which the blood may become quite normal, but which are always followed by relapse. There may be as many as five such remissions before death finally ensues.

Hemoglobin.—In 71 per cent. of the cases, the hemoglobin percentage was relatively high—*i. e.*, the amount per corpuscle was increased, although the total amount was of course very low. This *relative* increase of hemoglobin is known as a *high color-index*. The color-index of normal blood being 1, that of cases of pernicious anemia may be as high as 1.7, while in most severe secondary anemias it is below 0.5.

In the remaining 29 per cent. of the cases, the color-index was low or normal, which means probably that these cases were improving when they were seen, since we not infrequently see a low color-index in periods of remission.

Qualitative Changes in the Red Corpuscles.—*Average Diameter.*—Usually the average diameter of the red corpuscles is increased. This was the case in 80 per cent. of the cases; in the remainder it was normal.

While the *average* diameter is increased, even in those cases where the largest forms of red cells (macrocytes) occur, there are always normal and small forms (microcytes) as well, though usually in smaller numbers than the large forms. Some of the latter may be as much as 20 μ in diameter, while the dwarf forms are sometimes barely 2 μ across.

Variations in Shape.—Very commonly, though by no means always, we find greatly deformed corpuscles in the blood; all but 12 of the cases showed these. In the 12 exceptional cases, some showed really normal shapes, while most of them exhibited only slight deformities. These deformities are in no way characteristic of pernicious anemia, but occur in all severe anemias.

Henry has called attention to the fact that many of the deformed corpuscles assume more or less of an oblong or *oval shape*. This, like the increase in size, may be interpreted as a tendency to regression toward the type of blood seen in lower animals (*e. g.*, in frogs).

A great number of other deformities are seen; battledore-shaped, pear-shaped, and star-shaped forms occur. In one case observed by the writer, all the corpuscles were sausage-shaped, looking at first sight like a lot of gigantic bacilli.

Ameboid movements in deformed red corpuscles are occasionally seen, either in the projecting points or in the corpuscle as a whole. They are usually slow, but sometimes so rapid as to remind one strongly of bacteria or animal parasites.

Rouleaux formation is often absent or slight.

Peculiar Staining Reactions.—As already mentioned, normal red corpuscles react readily to acid stains and feebly to basic ones. Stained with hematoxylin and eosin, they take up only the eosin; with Ehrlich's triacid mixture, only the orange G. In pernicious anemia, on the other hand, some of



FIG. 157.—Pernicious anemia: L, L, lymphocytes; m, m, megaloblasts; cover-slips stained with Ehrlich's triacid, and drawn with camera lucida.

the red cells may have their affinities so modified that they take up a mixture of acid and basic stains, becoming purple with eosin-hematoxylin and purplish brown with Ehrlich's stain. This condition is very frequently seen in nucleated red corpuscles. It is easily simulated by conditions due to faulty technic. Spots in the corpuscle may have a different staining affinity from the surrounding corpuscle, so that they can be counterstained.

Nucleated Red Corpuscles (Erythroblasts).—Long recognized as a feature of the blood in pernicious anemia, the importance of this form of immature corpuscle as something peculiar to the disease has been of late considerably obscured by the fact that cells in many respects similar are found in a great variety of secondary anemias, as well as in leukemia. This confusion has been mitigated in some degree by the differentiation of two subvarieties of nucleated red corpuscles, viz.: (1) normoblasts, (2) megaloblasts.

The former of these was identified especially with cases of secondary anemia (posthemorrhagic, postmalarial, cancerous, etc.), while the latter was

thought to be characteristic of pernicious anemia. Ehrlich insists especially on this distinction. While recognizing that normoblasts were occasionally found in pernicious cases and megaloblasts occasionally in secondary cases, he yet asserts that in pernicious anemia the majority of all the nucleated corpuscles present are megaloblasts, while normoblasts are relatively infrequent. In secondary cases, on the other hand, normoblasts predominate.

Normoblasts are described, by Ehrlich and others, as red cells of normal size, containing a small nucleus, which stains intensely; megaloblasts as much larger than normal, and possessing a very large, pale-stained nucleus. Ehrlich believes the latter form of erythroblast to be characteristic of the fetal type of blood formation, while the normoblast represented the normal adult method of blood regeneration. Hence it is the latter that is found in the blood after hemorrhage; indicating that in the rapid regeneration of red corpuscles called forth in the healthy marrow by the loss of blood, a few immature cells are accidentally pushed into the circulation before losing their nuclei.¹

When, on the other hand, we find megaloblasts preponderating in the blood, as in pernicious anemia, it points, according to Ehrlich, to a reversion to an earlier and less fruitful type of blood formation—the fetal type.

This division by Ehrlich of erythroblasts into normoblasts and megaloblasts, and the significance which he attaches to them, fit the facts perfectly in perhaps three-fourths of all cases. That is to say, in the great majority of all cases of secondary anemia, we find cells corresponding to his description of normoblasts, and very few if any megaloblasts; while, in most cases of pernicious anemia, we find that the number of normoblasts present is much smaller than the number of megaloblasts. Now and then, however, a case occurs which does not correspond with Ehrlich's description. We may find nucleated corpuscles not corresponding to either of Ehrlich's types. Indeed, the writer has seen one or two cases in which not one of the many nucleated corpuscles present could be classed either as a normoblast or a megaloblast. This fact has been interpreted by Askanazy to mean that the normoblasts are simply *old megaloblasts*, the same cell passing gradually from one form to the other. He scouts entirely Ehrlich's idea of two types of blood-formation and of the different prognostic significance of the two varieties. In this he has been followed by many recent German writers, especially those who have not personally examined the blood of many cases. But Schaumann, Thayer, and most of those who have first-hand knowledge of any considerable number of cases are convinced of the fundamental truth of Ehrlich's view as to the different prognostic import of the two varieties of erythroblasts. His idea of blood-formation by extrusion of the nucleus has been generally abandoned, but is not the main point of his doctrine. The recent studies of Pappenheim² have gone far toward vindicating Ehrlich's idea of the essentially different nature of normoblasts and megaloblasts. The apparent "transition" forms not classed under either rubric, he considers as the older or younger forms of one or the other variety. The small, dark, structureless nucleus characteristic of normoblasts is in fact a typical old nucleus, and the large pale

¹ Ehrlich supposed the nuclei of normoblasts to be extruded and then to give rise to new red corpuscles. Pappenheim has shown that this is not the case.

² *Inaug. Dissert.*, 1895, and *Virchow's Archiv*, vol. cxlv., 587-648, 1896.

nucleus with clear and delicate nuclear structure (Ehrlich's "megaloblast") is in fact a young nucleus.

As a rule, we find only *old* normoblasts and *young* megaloblasts, the latter being so fragile and vulnerable that their nuclei rarely grow to maturity; while the former, representing the stable adult type of blood-formation, are much more likely to mature before getting into the blood. Occasionally, however, we do find young normoblasts (*i. e.*, with large light nuclei) or old megaloblasts (*i. e.*, with relatively small dark nuclei), and thus the supposed transitional forms of Askanazy are accounted for. The real distinction between a normoblast of any age and a megaloblast of any age is really in the character of the nuclear network; and this is not ordinarily seen with the stains used for clinical or routine pathologic work, as described in this article. But as, fortunately for us, we seldom see anything but small old normoblasts and large young megaloblasts, and as the marks of age and size are fairly easy to make out with ordinary technic, we are quite safe in considering all overlarge cells with young nuclei as megaloblasts, and all small cells with old nuclei as normoblasts. For the atypical forms occasionally seen, we must fall back upon the size of the whole cell as the best guide in clinical work.

One hears now and then of cases of pernicious anemia with no nucleated red cells at all in the blood. It is not impossible that such a condition may exist for a day or two, but in the vast majority of cases a patient search will show a few nucleated forms at all times, and plenty of them most of the time. They were present in every one of the cases examined by the writer more than once (107 cases), although sometimes hours of search were needed to disclose them. All of Schaumann's 38 cases and of Billing's¹ 20 cases showed nucleated forms. The writer has never been able to see any correspondence between the severity of the case and the abundance or paucity of erythroblasts. In his cases the number has varied from 3 to 7100 per c.mm. of blood, or from 2 to 6500 in every 1,000,000 red cells.

Ehrlich describes a case of fatal posthemorrhagic anemia in which he could find no nucleated corpuscles whatever. Autopsy showed that no regenerative effort had been put forth by the bone-marrow (*vide infra*, p. 466). There was no transformation of yellow (fatty) marrow into red (lymphoid) marrow, such as is almost invariably the case after traumatic or experimental hemorrhage. According to Ehrlich, therefore, a scarcity of nucleated red cells in pernicious-anemia cases would indicate the same lack of response on the part of the bone-marrow as was demonstrated in this case of secondary anemia.

But be this as it may, the cases with fewest erythroblasts are not the most severe, nor are those with most numerous erythroblasts any milder in type. This does not necessarily contradict Ehrlich's hypothesis, since there is abundant evidence that it is not simply or even chiefly the lack of red corpuscles that does the mischief in pernicious anemia. One patient with only 500,000 corpuscles per c.mm. may be up and about and do some work, while another patient with 1,800,000 may die. *It is not the anemia that is pernicious.* The anemia simply reflects very roughly the deeper underlying disease.

As to the kind of erythroblast, the writer's cases have with a single

¹ *Transactions Assn. Amer. Physicians*, vol. xv., p. 332, 1900.

exception, all shown a great preponderance of megaloblasts over normoblasts, the proportion being about 4 to 1 on the average.

In the remissions of the disease, nucleated corpuscles disappear from the blood simultaneously with the deformed, oversized, and abnormally stained varieties.

On the whole, then, although the presence of nucleated red corpuscles usually indicates an appeal to the marrow for more corpuscles (anemia) and hurried or faulty production there on account of the increased demand, we must not let ourselves be carried away by any gross mechanic theory, such as that the nucleated forms are simply carried along into the blood by the rush of newly formed cells hurrying to the rescue of defeated comrades. For we not infrequently find nucleated red cells in the blood when there is no loss of red cells to be compensated, no anemia to be cured. Thus, Ehrlich reports the finding of large numbers of nucleated forms in hemorrhagic small-pox, acute phosphorus poisoning, and chloroform icterus, with no anemia; and in the early stages of many cases of leukemia, when no anemia is present, enormous numbers of nucleated erythrocytes are seen.

White Corpuscles.—A great diminution of the number of leukocytes is the rule in all severe cases. Frequently less than 1000 are found in a cubic millimeter of blood. This is the more striking because, in other varieties of severe anemia, the leukocytes are usually normal or increased in number. In the remissions of the disease, the leukocytes rise with the erythrocytes and often go above the normal figure.

The differential count of leukocytes shows usually a striking decrease in the polymorphonuclear neutrophiles, giving rise to a considerable relative increase in the lymphocytes. In one of the writer's cases the lymphocytes rose to 79 per cent., and in another to 71 per cent.; the average in 110 cases was 45 per cent. as against the normal 30–35 per cent. Usually this increase is especially in the smaller forms. The eosinophiles average about 2.5 per cent., practically normal. A notable feature of the blood of pernicious anemia is the nearly constant presence of small percentages of myelocytes. These cells were seen in 80 per cent. of the cases, averaging about 2 per cent. of the leukocytes present. They are also seen in severe secondary anemia and in leukocytosis from any cause.

Occasionally we see basophiles, lymphocytes with neutrophilic granulations, and other anomalous forms, of which further account will be given under leukemia. Blood-plates are greatly diminished.

So much for the morphology of the blood in pernicious anemia. The amount of water in the blood is greatly increased and the solid constituents diminished, although the reduction of the amount of albumen in the serum is less than might be anticipated. In this respect it contrasts with most cases of anemia due to hemorrhage or malnutrition, in which the serum itself is greatly thinned. The blood in pernicious anemia, then, is *not* hydremic in the sense that the serum is watery, but simply contains an increased amount of relatively normal serum.

The Central Nervous System.—**The Brain.**—The general tendency to the extravasation of small quantities of blood is especially marked in the brain and meninges. The clots organize and remain as pigmented membranous spots in the meninges; in the brain itself, the site of the hemorrhage is marked by a collection of pigment, with vacuolization, edema, and diminished affinity for carmin stains.

Changes in the Spinal Cord.—Practically every case of pernicious anemia shows lesions in the spinal cord postmortem, whether these have given rise to symptoms during life or not. Out of upward of 40 cases on record, the writer can find but one (that of Burr) in which no changes were discoverable. The association of anemia and spinal-cord lesions cannot, therefore, be considered accidental.

The distribution of the lesions is usually symmetric or nearly so. The portion of the cord especially affected is that occupying the cervical and dorsal regions; "the lesions progressively decrease in intensity and extent at lower and lower levels of the cord, until in the lumbar region there is no disease at all, or it is extremely slight" (Burr). There are occasional exceptions to this. The gray matter is usually unaffected, the favorite seat of the lesions being in the posterior columns, especially in Goll's and Burdach's columns. The disease may be confined to this locality, and it is almost always more severe there than elsewhere. In some cases the lateral columns in and



FIG. 158.—Section of spinal cord, upper dorsal region, from a case of pernicious anemia (Burr).

near the pyramidal tracts are also somewhat affected, and rarely the direct cerebellar tract as well. "Almost invariably there is a band of normal white tissue separating the diseased area in the posterior columns from the gray matter" (Burr). In the cervical region, there are often two separate areas of sclerosis within the posterior columns. No gross deformities or alterations in the shape of the cord are produced, the disease contrasting in this respect (and in its cervical localization) with tabes. Occasionally hemorrhages in the cord are found, as in the cases of Petion,¹ Lenoble,² and Teichmüller.³ The latter describes hemorrhage into the anterior fissure and numerous minute foci of blood in the gray matter, as well as in the anterior and lateral columns. This case also showed increase of neuroglia and thickening of the vessels and the usual degeneration of the posterior columns. Teichmüller inclines to the view that all the lesions are primarily due to hemorrhages. Nonne thinks that the earliest stages of the process consist of minute foci of acute myelitis.

¹ *Nord. Med. Ark.*, N. F., vi., 1896.

² *Revue de Méd.*, June 10, 1897.

³ *Deut. Zeit. f. Nervenheilk.*, viii., 1896.

Bastianelli divides the cord lesions of pernicious anemia into three groups: First, those occurring in rapidly fatal cases, where the nervous symptoms are slight or absent and are overshadowed by the symptoms of general anemia; such cases show irregularly scattered foci of degeneration, chiefly in the posterior columns, some in the lateral columns. Second, cases of slow clinical course, in which the nervous symptoms (paralysis, etc.) appear earliest, and later the anemia is noticed; in such cases the lesions agree with the suggestion of the symptoms and are more continuous and extensive. Third, cases in which the lesions are mainly due to multiple minute hemorrhages, as suggested by Teichmüller. "The condition is not systemic; that is, it is not confined to any one tract or set of tracts, but overlaps boundaries" (Burr).

The great majority of writers on the subject agree in considering the lesions as a manifestation of toxemia, and therefore similar to the lesions found in diphtheria, pellagra, ergotism, and diabetes.

This conclusion is the more natural in that it has been shown of late years that, despite the lack of red corpuscles, there is no lack of oxidation

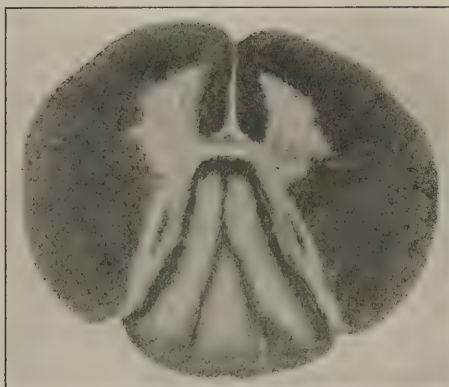


FIG. 159.—Section of spinal cord, cervical swelling, from a case of pernicious anemia (Burr).

in the tissues. There is hyperoxidation rather than diminished oxidation, and no theory of oxygen starvation can be used to explain the cord lesions.

A very slight degeneration of the posterior peripheral nerve-roots is sometimes found, and in von Noorden's case the tibial and peroneal nerves also showed degenerative changes.

The histologic changes vary according to the age of the lesions. Those most recent show normal axis-cylinders with swollen and granular myelin sheaths and no changes in the interstitial substance. In the older portions, there is great increase of neuroglia and of nuclei with space-formation. The sheaths and axis-cylinders are shrunk or gone, and there is often a honey-combing of the tissue, the spaces being empty, or full of clear homogeneous substance. In the connective-tissue network, numerous corpora amylacea may be seen. The walls of the vessels may be thickened and hyaline.

Fatty Degeneration of Various Organs.—The heart shows extensive fatty changes in almost every case. As a whole, it may be so flabby that, if held by the apex in an upright position, it collapses so as to

cover the hand that holds it. The endocardium, particularly over the papillary muscles, shows a yellow mottling, the so-called tabby-cat or wren's-breast mottling. The changes are usually most marked on the papillary muscles of the left ventricle, possibly because this is where the greatest strain falls in the work of the heart. The whole organ is occasionally hypertrophied and dilated; but, as a rule, it is normal or undersized.

Under the microscope, the cross-striation and nuclei are gone; and in the place of the former, fat-drops are arranged in rows, "like pearls on a string." These changes, however, are not in any way peculiar to pernicious anemia; any variety of secondary anemia, even the acute posthemorrhagic types, may exhibit similar lesions.

The heart's blood is often found partially fluid many hours after death. A few pale, loose, friable clots may be found. The aorta is usually of normal size. Fatty degeneration of the capillaries, especially in the brain, may be extensive.

The kidneys are intensely pale throughout and uniformly yellowish. The capsule is not adherent. The organ is very soft and greasy. Microscopically intense fatty and granular degeneration is found, especially in the convoluted tubules. Small hemorrhage may be seen under the capsule or microscopically in the glomeruli. Deposits of pigment containing iron are occasionally to be found (*vide infra*).

The liver is sometimes enlarged, always very pale, and microscopically shows extensive fatty changes. The deposit of iron in the organ is mentioned on page 458.

The pancreas occasionally shows fatty degeneration.

These lesions were formerly attributed to suboxidation of the tissues, owing to the supposedly great diminution in the oxygen-carrying power of the blood. But, since it has been shown by von Noorden and others, as above mentioned, that the blood somehow manages to carry all the oxygen needed by the tissues,¹ some other explanation must be sought. While nothing positive is known as to the cause of the fatty changes, it is natural to suppose that they are similar to those occurring in diphtheria and in phosphorus or arsenic poisoning, thus bringing them into relation with the changes in the blood and spinal cord as the direct results of a common toxic cause.

Apparently there is no parallelism between the severity of the anemia and the extent of the fatty changes (Krehl).

Changes in the Bone-marrow.—While there is reason to believe that the fatty changes in the parenchyma of the organs, like the lesions in blood, stomach, and spinal cord, represent relatively direct effects of the unknown poison, the marrow-changes appear to be secondary or due to an effort at repair, such as causes hypertrophy of the heart after antecedent changes in the valves.

In a certain number of cases, no such changes are found; the marrow presenting at times no alterations at all, at times only such as are common to various chronic diseases. Cases in which no changes are found in the marrow are usually those in which clinically no nucleated red corpuscles appear in the blood, indicating an absence of effort at regeneration. Especially rapid cases sometimes show no marrow-changes.

When changes do occur, they consist macroscopically of a transformation of the fatty marrow normally found in the shaft of the long bones of adults,

¹ In health, apparently only part of the oxygen-carrying power of the corpuscles is used.

into red or "lymphoid" marrow, similar to that found in the epiphyses normally, or in the whole shaft in late fetal life. The red marrow is often compared to currant jelly, the consistency probably being in mind as much as the color, for in well-marked cases the marrow may be almost fluid. So far as gross appearances go, the marrow is identical with that found in any severe secondary anemia or after experimental bleeding in animals.

But microscopically we find what Ehrlich has termed "megaloblastic degeneration." In the red marrow of experimental anemia, the red color is due to the replacement of fat by red corpuscles, chiefly nucleated and of the normoblast type; that is, the diameter of both nucleated and nonnucleated forms is approximately normal. In pernicious anemia, on the other hand, the majority of the corpuscles are oversized and those with nuclei are of the megaloblast type (*vide supra*). Many of the nuclei show signs of karyokinesis, but in the majority the nucleus is in one of the conditions known as karyorrhexis and karyolysis; that is, it is breaking up or fading out.

While the average diameter of the red corpuscles is usually increased (as in the circulating blood), there is a very great variation in their size—i. e., from 3 μ to 17 μ in diameter—and also in the amount of hemoglobin in the cell. In this respect, however, the conditions of the normal epiphyseal marrow are but slightly exaggerated; for we find there great differences in size and in the amount of hemoglobin in any red marrow. The writer always gets the impression, in examining such marrow, that he is in the workshop, where all stages of the unfinished product are to be seen.

The marrow-leukocytes are less numerous than usual, but not otherwise abnormal, except that the number of the giant leukocytes of the marrow is increased. Such cells often take up several red corpuscles. The amount of pigment in and between the cells is increased.

Red marrow may be present in spots or islets in the shaft of the bone, or may occur in the whole space. The tibia usually shows such changes well. Schaumann found they were absent in the ulna and radius of cases in which the humerus and femur showed them well.

Smear-preparations show the finer changes much better than sections. A drop of the semifluid marrow is spread between two cover-glasses in the manner explained above, and then heated and stained like a blood-film.

The spleen and lymph-glands show no changes, in the majority of cases. Now and then we meet with splenic enlargement, and the writer has twice seen this so great as more than to double the normal weight of the organ. The spleen is usually soft and the pulp increased in volume. Microscopically no changes of special significance, except a deposition of iron-pigment, are present.

Increase of Iron in Various Organs (*Siderosis*).—The liver, kidneys, spleen, and bone-marrow are the organs especially concerned; occasionally also the pancreas and lymphatic glands.

The amount of iron contained in the liver may be as much as 23 times the normal quantity. The iron-pigment is distributed chiefly in the cells of the outer and middle zones of the hepatic lobules. This distribution is believed by Hunter to be characteristic of the disease. Iron-pigment is also deposited in the leukocytes and the endothelium of the capillaries, but this is apparently of no special significance. The presence of the metal may

be demonstrated by a solution of ammonium sulphid, which, combining with the iron to form the black sulphid of iron, at once blackens the tissue. Liver sections can also be stained so as to exhibit very beautifully the distribution of the pigment, by being soaked for several hours in a solution of ferrocyanid of potash, and then in dilute hydrochloric acid for an equal time. The areas containing iron-pigment are stained blue (Prussian-blue reaction).

In the kidney, spleen, pancreas, and marrow, the increase of iron is much less marked than in the liver.

Atrophy of the Gastric and Intestinal Mucous Membrane.—

The changes in the secreting tubules are at times so marked that they have been supposed by some of the earlier writers on the subject to be the source of the other lesions—*i. e.*, to be the “cause” of the disease through inanition. But many cases show at autopsy no such changes, and in the vast majority there are periods of good digestion throughout the clinical course of the disease, such as could not exist if the digesting functions were destroyed or greatly impaired. It is much more likely that the atrophic condition of the gastro-intestinal mucous membrane which is found in a certain percentage of autopsies is secondary to the lesions already described.

The changes may be macroscopic or only microscopic. In some instances the whole gastro-intestinal tract shows a striking thinness, smoothness, and transparency; at times this is seen only in the stomach. In other cases the wall of the stomach is tough and opaque from interstitial hyperplasia.

Microscopically we may find: (*a*) Fatty degeneration of the secreting tubules; (*b*) complete destruction of epithelium, with reactive hyperplasia of the interstitial tissue; (*c*) the whole glandular mucosa may be gone, leaving only a lining membrane of flattened epithelium and reducing the thickness of the wall to one millimeter; (*d*) overgrowth of connective tissue in the mucous membrane and submucosa, especially the latter—its vessels may be thickened; the tubules are compressed and distorted as in ordinary interstitial gastritis; (*e*) Lubarsch found numerous eosinophile-cells and also masses of oxyphilic extracellular granules embedded in the interglandular tissues; (*f*) degeneration of the motor nerves of the intestine and of its muscular layer has been reported by several observers (Jürgens, Sasaki, and Blaschko). All these changes have been observed in diseases which run their course without extreme anemia—*e. g.*, mammary cancer, chronic lead poisoning.

Hemorrhages.—A striking feature of the autopsy of some cases of pernicious anemia is the presence of numerous punctate hemorrhages, seen especially on serous surfaces, as in the pericardium, but also on mucous membranes and in the skin. During life they are frequently observed in the retina. Their occurrence in the spinal cord has already been mentioned. Hemorrhage into the substance of the spleen is an occasional occurrence and may produce considerable enlargement of the organ. The cause of these various hemorrhages is unknown; they have been attributed, on insufficient evidence, to embolism and to degeneration of the capillary walls.

Other Changes.—The yellow color of the skin, so characteristic of the disease during life, is also very marked in most cadavers. It is a peculiar pale straw color, not unlike the tint of manilla paper, and very evenly distributed throughout the body. The bright lemon-yellow of the subcutaneous fat, as well as the amount of the latter, is often striking. Patients do not emaciate, provided they are able to take a fair amount of food, as some

of them do to the very last. In about one-third of the cases, considerable emaciation is seen, probably as the result of anorexia and poor assimilation of food; but in the remainder the fat-layer is well preserved and its color is near an orange tint. The bright-red color of the muscles also attracts attention in many cases.

Although it is probable that the altered color of the skin, fat, and muscles is connected in some way with altered blood-pigment from the destroyed red corpuscles, we have no positive evidence that this is so. The colors are in no way the result of simple bloodlessness, which causes only pallor of the affected parts. This pallor is very striking in the lungs and stomach and is noticeable in all the organs.

Summary.—*Relatively primary changes:* (a) Great oligocythemia, with high color-index, enlarged and nucleated erythrocytes, no leukocytosis; (b) sclerosis of the posterior and lateral columns of the spinal cord; (c) fatty degeneration of various organs, especially of the heart. *Relatively secondary changes:* (a) Megaloblastic degeneration of the bone-marrow; (b) increase in the amount of iron in the liver and elsewhere; (c) atrophy of gastric and intestinal mucous membrane; (d) punctate hemorrhages in serous membranes and elsewhere; (e) pallor of all organs, discoloration of skin, fat, and muscles.

CHLOROSIS.

Definition.—A disease occurring exclusively in young women, usually between the seventeenth and twenty-third years, characterized by symptoms of anemia and by a great reduction in the amount of hemoglobin in the red blood-corpuscles.

Etiology.—Despite the frequency of its occurrence and the great activity of speculation concerning it, we are entirely ignorant of the real cause of chlorosis. Probably no disease has ever called forth a greater number or variety of unsatisfactory hypotheses. It has been attributed to changes in the gastro-intestinal organs, such as auto-intoxication from constipation, deficient formation of hemoglobin in the intestine, gastroptosis, dilated stomach, etc. (Clark, Forchheimer, Meinert, and Pick). Theories of a nervous origin are common, either referring the disease to mental or nervous shock, strain or overexertion, or looking upon it as a neurosis of the vasomotor and sympathetic nervous system. Vascular hypoplasia, especially of the aorta, has been supposed to cause the trouble (Virchow). Genital anomalies or disturbances in the function of the genital organs have been thought to be of etiologic significance (Rokitansky, Trousseau). Chlorosis has been considered an infectious disease, owing to the occasional slight enlargement of the spleen and occurrence of fever. Hayem and the French school generally stick to the theory that chlorosis is due to a lack of development of the hematoblasts (for such Hayem considers the blood-plates to be) into red corpuscles. Bunge's theory of iron-starvation through a combination taking place between the iron of the ingested foods and the sulphur of abnormal intestinal fermentation is exceedingly ingenious, but has been conclusively disproved, since there is no evidence of any abnormal intestinal fermentation.

Without enlarging this list of conflicting theories any further, we may now point out some of their difficulties. The constipation theory will not explain the cases, not at all rare, in which no constipation exists. Intestinal

fermentation is not greater than normal, as Rätthen and Mörner have shown; gastroptosis is present in only about one-third of the cases, and dilated stomach still less often. Many cases arise without any nervous shock or strain whatever, and the evidence of a neurosis as part of the disease does not tend to show that this is the cause of it. Hypoplastic arteries are often found at autopsy where no chlorosis existed; and the use of iron, while curing the disease, cannot be supposed to enlarge the aorta, as it should if small vessels caused the disease. Genital anomalies are present in only a moderate percentage of cases; and, where present, no reasonable connection has been shown between them and the disease itself. Evidence of infectious origin (enlarged spleen and fever) is absent in most cases.

Hayem and his school stand alone in their belief that red cells are developed from blood-plates; but many modern observers hold the belief that defective hemogenesis is the cause of the disease. No evidence of increased hemolysis, such as can be shown in pernicious anemia, exists in chlorosis; and the corpuscles bear, as we shall presently see, some marks of being defective from the start.

Why the hemogenetic power is deficient, and what the connection is between the defective blood-making and the particular age and sex at which the disease occurs, are questions to which no answer can as yet be given. It has been suggested that the age at which the disease occurs corresponds to the "interregnum" between the end of the functional activity of the thymus gland and the establishment of the function of the ovaries, and that the absence of the influence of one or another of these organs is deleterious in some way to the organism and the blood. But chlorosis usually begins several years after the establishment of the menstrual function, and castrated women do not become chlorotic. The thyroid gland has been observed to be enlarged and sometimes tender in chlorosis, and some connection with the symptoms has been assumed to exist.

Biernacki has recently pointed out that too much stress has been put on the lack of hemoglobin, in our conception of the disease. The severity of the cases is not in proportion to the lack of hemoglobin, and the amount of iron in the blood is often normal.

In conclusion, it may be said that any satisfactory theory of the nature of chlorosis must take account of the following facts: That it is usually curable by the use of iron, hence it cannot depend on any gross anatomic lesion; that it is closely connected in some way with the period of life immediately following the establishment of the menstrual function; that the blood-changes do not differ essentially from those of many cases of ordinary symptomatic anemia and are not directly proportional to the severity of the symptoms.

Pathologic Anatomy.—Autopsies are so rare that but little is known of the lesions of chlorosis, all the less because in the few recorded autopsies there has been very little to see. We will begin, therefore, with the tissue the pathologic changes of which we can follow during life, viz.:

The Blood.—I. *Gross changes.*—In some cases, if a vein be punctured, blood will spurt from it as from an artery; and in many cases we note how very easily the blood flows from a needleprick. The pallor of the drop is often as great as or greater than in pernicious anemia. Coagulation is rapid, although the amount of fibrin is usually not increased. Many writers believe that the blood-mass is increased ("plethora serosa").

The specific gravity is always reduced and is in direct proportion to the reduction in hemoglobin.

II. *Microscopic Changes.*—(a) *Quantitative Changes.*—The number of red corpuscles in early cases is normal or approximately so; only in neglected cases, when the anemia has been allowed to progress untreated for a considerable time, does the count of red cells fall considerably. In neglected cases of long standing, we occasionally see very low counts. Stengel records one of 1,500,000 per c.mm. The lowest in the writer's experience is 1,932,000. Of 77 cases of which he has records, only 11, or one-seventh, showed a reduction of red cells below 3,500,000. On the other hand, it is not at all infrequent to see an actual increase. The writer has counted cases with 7,100,000, 5,884,000, and 5,620,000 red corpuscles to the cubic millimeter. The average count in his series was 4,050,000, and in Thayer's 4,096,544.

Hemoglobin, on the other hand, was reduced in the writer's series to 41 per cent. on the average; in Thayer's cases it averaged 42.3 per cent. Six of the writer's cases had less than 20 per cent. of the normal amount of hemoglobin (Fleischl). The color-index averaged 0.50—in striking contrast with that of pernicious anemia (1.04 in the writer's cases).

If any diminution in the number of red cells occurs, it takes place subsequently to the fall in the percentage of coloring matter; and conversely, in convalescents, the number of corpuscles reaches normal before the hemoglobin, as is the case in all anemias.

White Corpuscles.—There is no leukocytosis in the great majority of cases; the average count in the writer's series was 7485, and only one-tenth of the cases showed any increase. Rarely there is a slight temporary increase, especially during rapid convalescence.

The blood-plates are always increased.

(b) *Qualitative Changes.*—Hayem was the first to notice that in severe cases the diameter of the red cells is usually less than the normal—*i. e.*, 6–7 μ , instead of 7.5 μ , the normal. In mild cases this change does not occur.

The shape of the corpuscles is usually unaltered, although in marked cases poikilocytosis may appear and even reach an extreme grade. In fresh or stained specimens the lack of coloring matter makes the centers of the corpuscles strikingly pale, so that only the rim appears colored.

Nucleated red corpuscles are found only after prolonged search, and then sparingly. Almost invariably such nucleated corpuscles as do occur are of the normoblast type; but it is on record that megaloblasts have been once seen by Hammerschlag and once by Ehrlich.

The white corpuscles usually show a marked decrease, absolute as well as relative, in the number of polymorphonuclear cells, with a relative increase of the lymphocytes, especially of the smaller forms. Eosinophiles are occasionally slightly increased, and in severe cases we may see a few myelocytes, as in any other severe anemia.

Attempts have been made to distinguish a myelogenous and a lymphatic form of the disease, but the distinction has not been established.

Chemically the blood shows an increased proportion of water, although the dried residue of the serum is practically normal in amount. The amount of albumin is always decreased, as are the phosphorus and potash.

Other Lesions.—The hypoplastic heart and aorta are passed down from

book to book as a lesion of chlorosis, on the basis of the older observations, although the number of recent cases in support of it is trifling. In some cases there is slight cardiac hypertrophy, which has been explained in various ways. The aorta is usually said to be thin, narrow, and elastic, with areas of fatty degeneration of the intima and irregular origin of the intercostal branches. Similar conditions are often seen where no chlorosis is present.

One certain fact concerning the circulatory system is the marked tendency to thrombosis, especially of the cerebral sinuses, less often in the veins of the extremities. Thrombosis practically never occurs in pernicious anemia; on the other hand, hemorrhages—retinal or other—are very rare in chlorosis. The weakness of the circulation is shown by the frequency of slight edema of the ankles.

The *genital organs* are not infrequently hypoplastic or infantile, the uterus and ovaries being small and undeveloped, the number of Graafian follicles deficient, the fundus of the uterus disproportionately small, the breasts undersized, the pubic hair deficient. On the other hand, the genitals may be quite normal and are sometimes even hypertrophied.

The blood-making organs show no distinctive changes; the spleen may be slightly enlarged.

In extreme cases, fatty changes in the liver, spleen, and pancreas have been noticed. Gastropptosis or general enteropptosis occurs in about one-third of the cases, and the stomach may be dilated. The gastric contents show various anomalies of secretion, hypersecretion being the commonest.

Summary.—Such lesions as have been noted in connection with chlorosis have probably no essential relation to it. Of its real pathology, as of its real etiology, we are entirely in the dark. The blood changes are well marked, but not in themselves distinctive; for, though strikingly different from those of pernicious anemia, they may be identical with those of symptomatic anemia due to well-known causes.

SECONDARY ANEMIA.

Etiology.—The most important etiologic factors are: Hemorrhage; malignant disease; chronic suppurations; nephritis; dysentery; cirrhosis of the liver; acute infectious diseases and syphilis; poisoning (lead, arsenic, bad air, intestinal parasites); pregnancy and lactation; blood destruction (malaria, poisoning by chlorate of potash, by phenacetin, etc.); Addison's disease; myxedema; rickets.

The Blood.—The red corpuscles may be greatly diminished. The most extreme diminutions are seen in malignant disease, chronic malaria, syphilis (congenital or acquired), rickets, and after typhoid fever. The corpuscles in such cases may fall to or below 1,000,000 per c.mm.; but such low counts are the exception and not the rule. In most cases of malignant disease or phthisis, at the time of death the corpuscles are not greatly reduced and the changes in the blood affect chiefly the quality and not the number of the erythrocytes.

The condition of the blood typical of the vast majority of moderately severe cases is precisely that seen in chlorosis, so far as the red cells are concerned—*i. e.*, there is a reduction in the albumin and hemoglobin per cell, the total count remaining approximately normal or being even somewhat

increased. One gets the impression in many cases that the total blood-mass is diminished; but this is not susceptible of verification, as a rule. The reduction in hemoglobin, though usually present, is often surprisingly slight, considering the pallor of the patient.

In severe cases the corpuscles may be deformed and undersized. An increase of the average diameter, such as appears in pernicious anemia, the writer has never seen.

Nucleated corpuscles may be present in any form of secondary anemia, but are usually found only after long search, except in the anemias of infancy, where they are relatively frequent. In most cases only normoblasts are found. Rarely megaloblasts are seen, always in smaller number than the normoblasts. Karyokinesis and karyolysis may be observed. The abnormal staining reactions described under pernicious anemia are less marked in secondary anemia, but do occur.

Leukocytes.—Leukocytosis may or may not be present. After hemorrhage, in most cases of extensive new growths, advanced phthisis, or other suppurative processes, the white corpuscles are usually increased, the increase taking place chiefly in the polymorphonuclear forms. The latter may be relatively increased, even where no leukocytosis is present. In rickets the mononuclear cells may predominate, and this is not infrequently seen after hemorrhage and rarely in malignant disease. In the latter the eosinophiles sometimes show a relative and absolute increase. Small percentages of myelocytes are frequently present.

The alkalinity and specific gravity of the blood are usually decreased, and the amount of water is proportionately increased. Potassium is decreased and sodium increased. Iron, according to Biernacki, is not reduced.

LEUKOCYTOSIS.

Leukocytosis is an increase of the number of leukocytes in a given quantity of peripheral blood, over the number normal for the individual concerned, this increase never involving a relative diminution in the number of the polymorphonuclear varieties, and usually a marked absolute and relative increase.

The element of time insisted on by Fitz and others is of no importance, as the leukocytosis may persist for years or only for a few minutes.

The above definition needs some explanation: it says "of the peripheral blood" to avoid deciding the disputed point whether leukocytosis may sometimes mean an actual increase of the leukocytes in the body, or whether it is always a migration toward the periphery from the internal organs; whatever is the truth, the number of cells in the peripheral blood is certainly increased. The number of leukocytes normal for the individual must be previously known or calculable—a normal child of four years has a sufficient number of leukocytes per cubic millimeter to constitute a leukocytosis for an adult whose normal count is lower; different adults also differ more or less from each other. We must include in our definition a statement of the kind of leukocytes the increase of which constitutes leukocytosis in contradistinction from leukemia (lymphatic or myelogenous), lymphocytosis, and eosinophilia. It is not the number, but the kind, of leukocytes present that enables us to distinguish leukemia from leukocytosis; the count of leukocytes in bubonic plague or in sarcoma or in pneumonia may be greater than in leukemia, but

the increase is made up by cells of a different variety. Lastly, in order to be sure that the polymorphonuclear cells are not decreased, we must know whether the patient is a child or adult, since the normal relative proportions of the different leukocytes are very different in the infant and in the adult.

Leukocytosis may be (a) physiologic, (b) pathologic.

Physiologic leukocytosis occurs in the newborn; during digestion; during pregnancy, parturition, and the puerperium; after violent exercise, massage, electricity, brief cold baths, prolonged hot baths; in the moribund state (terminal leukocytosis).

The following table, compiled from the best authorities and from personal observation, illustrates the leukocytosis of the newborn:

Age.	Leukocytes.
At birth	17,000-21,000 (26,000-36,000 after first feeding)
End of first day	24,000
End of second day	30,000
End of fourth day	20,000
End of seventh day	15,000
Tenth day to about the tenth year	12,000

Digestion leukocytosis is present in most healthy individuals after a proteid meal, reaching its maximum in about three hours. The count is increased about 33 per cent. over the normal number. The normal percentages of the different varieties of leukocytes may remain the same, or there may be an absolute and relative increase of the lymphocytes. In gastric cancer and other chronic gastric trouble, digestion leukocytosis is usually absent.

Most primiparæ show, during the later months of pregnancy and after parturition, a leukocytosis of about the same extent as the digestion leukocytosis. It reaches higher figures at the time of parturition (often 15,000-20,000), and persists, as a rule, for at least a week afterward. The neutrophils alone, or all varieties of leukocytes, may be equally increased.

A number of influences acting on the vasomotor system, such as exercise, massage, and baths, raise the leukocyte-count about 33 per cent.

Near the end of many chronic diseases the leukocyte-count rises rapidly. This is especially marked in pernicious anemia, and may give rise to the mistaken idea of a transition to leukemia.

Pathologic leukocytosis may be divided as follows: Posthemorrhagic, inflammatory, toxic, and due to malignant disease or to therapeutic or experimental influences.

Posthemorrhagic leukocytosis may appear immediately after a hemorrhage or not till twenty-four hours or more have elapsed. It is moderate in degree (15,000), and may be a true leukocytosis or a lymphocytosis (*vide infra*).

Inflammatory leukocytosis appears associated with inflammations of all kinds, when neither the infection nor the resistance of the organism is easily victor in the struggle. The leukocytosis is of greater extent in virulent processes, whatever their cause and whether extensive local lesions are present or not. The count in severe cases of pneumonia or peritonitis may run as high as 100,000 per c.mm., 90-95 per cent. being usually of the polymorphonuclear variety.

Toxic leukocytosis is seen in such affections as illuminating-gas poisoning, uremia, ptomain poisoning (decayed fish), blood destruction (through the influence of free nuclein), quinin poisoning, during etherization, in gout, etc.

Most cases of extensive malignant disease, of whatever nature and situation, are associated with leukocytosis. Small growths, such as carcinoma of the stomach or the lip, do not produce, as a rule, any increase of leukocytes.

Salicylates, antipyretics, pilocarpin, nuclein, tuberculin, spermin, ergotin, injections of normal salt solution, and many other therapeutic measures raise the leukocyte-count.

An important group of infectious diseases is distinguished from all other infections by *not* producing leukocytosis. These are: Typhoid fever, malaria, influenza, measles, tuberculosis (unmixed infections, except meningeal cases), leprosy.

In typhoid fever, miliary tuberculosis, pernicious anemia, and many cases of malaria, the leukocytes are diminished.

Lymphocytosis.—This is a relative or absolute increase of lymphocytes in the peripheral blood. The condition is physiologic in infancy; and in many diseases of infancy, especially in those affecting the gastro-intestinal tract, it becomes very marked.

Rickets, syphilis, scurvy, some cases of malignant disease, chlorosis, pernicious anemia, chronic malaria, and other causes of cachexia may produce lymphocytosis. It may be seen after hemorrhage and in any condition of marked debility.

Eosinophilia.—This is a relative or absolute increase of eosinophiles in the peripheral blood. It is found in trichinosis and other diseases due to animal parasites, such as malaria, beriberi, ankylostomiasis; in bronchial asthma after tuberculin injections; in certain cases of sarcoma and in osteomalacia; in pemphigus, pellagra, dermatitis herpetiformis, and other skin diseases.

Theories of Leukocytosis.—The majority of modern writers agree in regarding leukocytosis as a manifestation of chemotaxis. A new production of cells can hardly be supposed, considering the rapidity with which the increase may appear and disappear. It probably represents a drawing-forth of the wandering cells from the capillaries of the internal organs, especially the bone-marrow. It is often preceded by a short period of diminution of leukocytes, or "leukopenia," in the peripheral circulation, during which time the cells heap up in enormous quantities in the lungs and other internal organs and are destroyed in considerable number, as maintained by Löwit. The occurrence of leukocytosis without inflammatory exudation upsets von Limbeck's theory that it forms a part of the process of emigration; and the fact that it does not occur in typhoid fever and it affects chiefly the polynuclear cells, and not the lymphocytes, disposes of Virchow's idea that it is due to stimulated glandular activity.

The prevalence of polynuclear cells is usually explained as due to their ameboid activity, which makes them quick to respond to chemotactic influence; but in many leukocytoses the polynuclear cells differ markedly in type from those seen in normal blood, and, if ameboid motion determined their migration to the surface, the eosinophiles, which are even more actively ameboid, should also increase.

To the mind of the writer, no theory of leukocytosis yet advanced suffices to explain all the facts.

LEUKEMIA.

The present state of our knowledge of this baffling and mysterious disease is perhaps best conveyed by considering it as characterized by the

presence in the blood and in the organs (in the form of tumors or irregular accumulations) of enormous numbers of leukocytes, either in the stage just before division ("theilungsreif") or just after division (small lymphocytes).

Under this general type there are recognized three subvarieties, each with a characteristic condition of the blood and of the organs—characteristic, that is, in being distinguishable from one another and from all other diseases except Hodgkin's disease. These three varieties of leukemia are: Chronic myelogenous leukemia (myelocythemia); chronic lymphatic leukemia (chronic lymphemia); acute lymphatic leukemia (acute lymphemia, lymphogonemia).

The first is characterized by the presence in the blood, in the nodules of the spleen and liver, of elements corresponding in morphology and relative proportion to the elements of the marrow; in the marrow the normal cells are greatly increased in number.

In the second, the blood, blood-making organs, and secondary nodules are flooded with elements corresponding to the small lymphocytes of normal blood and lymph.

The third shows chiefly a heaping-up in the blood, marrow, lymphadenoid structures, and visceral nodules, of cells corresponding to those seen normally in the germ-centers of the lymph-glands and to the large lymphocytes of the blood. These cells are lymphocytes ready for division ("theilungsreif"). Benda applies to them the term "lymphogonie." Following this terminology, we might call the condition of the blood "lymphogonemia."

Intermediate varieties, especially between the second and third of these divisions, are not infrequently observed. The more acute the case, the more nearly does it preserve the type described in the third division.

Causation and Pathogenesis.—As to the primary cause of the disease, we are utterly in the dark. All we know about it is that it results in a great acceleration of the process of cell division among the leukocytes and increased facilities for the entrance of the leukocytes so produced into the circulating blood. Without this last factor we have no leukemia, but only a pseudoleukemia (Hodgkin's disease).

The question as to whether the disease is primarily one of the blood, and secondarily of the blood-making organs, or *vice versa*, is generally decided in favor of the second view by the fact that mitoses are found almost exclusively in the organs, and only exceptionally in the blood. This is taken to show that the process does not originate in the blood, but that the blood-making organs are relatively the primary seat of the process.

That the unknown stimulus which excites these organs to greater activity is in all probability brought there in the first place by the blood or lymph, and does not originate in the organs themselves, does not prevent us from thinking of the blood as a secondary feature so far as the actual production of the new leukocytes is concerned. There is no good reason for supposing that the leukocytes are formed in the blood and carried thence to the "blood-making" organs; all the evidence points the other way. But, as has been pointed out by Müller, Hindenburg, and others, the capillaries of the liver and the lymph-passages of lymphoid organs are in leukemia great breeding-places for leukocytes. Probably a far larger number is produced here than in the germ-centers of the lymphoid organs themselves. These "breeding-places" may be said to stand midway between the freely circulating blood and the relatively solid and static tissues of the lymphoid organs. Such a stimulus has been somehow applied to the leukocyte-producing process that it

will go on in any slowed circulation, such as in the liver-capillaries, although the still slower circulation of the marrow and other lymphoid organs can also furnish the requisite conditions for cell division, and even in the rapid peripheral circulation mitosis occasionally occurs.

It has already been said that we rarely find in the blood or in the other tissues any relative excess of those cells which are usually considered more or less mature (polymorphonuclear neutrophiles, eosinophiles). Hence it has been supposed by some that the increased number of the other (young?) varieties was due in part to a delayed metamorphosis of the cells produced, as well as to an overproduction. That there is an increased production there can be no reasonable doubt; but whether or not the factor of retarded development plays a part, we are not as yet in position to decide. The great rapidity of cell destruction (witnessed by the increased uric acid in blood and urine), without decrease and often with increase of the leukocytes in the blood, would make it somewhat unlikely that the life of the individual cell is prolonged; and the large amount of leukocyte débris seen in all the organs is also against a prolongation of cell life. Such prolongation could at best account for little increase, since the supposed "mature" forms are absolutely much increased in some types of the disease, although hardly ever relatively increased.

As said above, there is nothing known as to the nature of the stimulus which produces such abnormal activity of the blood-making organs. It has been supposed to be of an infectious nature; but the great majority of cultural experiments have been negative, and where positive the result is to be explained as an accidental invasion of the diseased tissues by organisms irrelevant to the causation of the disease itself. The questions regarding the increased facility with which leukocytes enter the blood is discussed on page 475.

As with pernicious anemia and chlorosis, the opinion is gaining ground that the blood changes, although characteristic and of great diagnostic value, are not what weakens and finally kills the patient; for the clinical severity of the cases is not parallel to the extent of the aberrations of the blood from the normal. The same is, however, to be said of the changes in the blood-making organs. They are not proportional to the clinical severity of the case; and patients with huge spleens, extensive blood changes, and presumably equally extensive gland and marrow lesions, sometimes feel perfectly well and live for two or three years, or until carried off by some intercurrent disease. Nothing is more striking than the utter disproportion between the clinical mildness of many cases and the extensive alterations of the blood, the disease often being discovered by accident when the individual feels perfectly well.

The conventional divisions of cases of leukemia into lymphatic, splenic, and myelogenous, or into lymphatic on the one hand and splenomyelogenous on the other, are no longer justifiable. There are probably no cases confined to any one, or even any two, of these three sets of organs. Probably in all cases, and demonstrably in many, the whole lymphadenoid apparatus, including the spleen and marrow, is affected. The spleen is largest in chronic cases; and most, though by no means all, chronic cases are associated with the prevalence of marrow elements in the blood and elsewhere. But the spleen may be as greatly enlarged in cases of chronic lymphemia where there is no prevalence of marrow elements, and no one any longer

supposes that there are any peculiar cells coming to the blood from the spleen. The spleen forms part of the lymph-apparatus; and though it doubtless has various other functions besides the production of lymphocytes, the same could be said of the lymph-glands, which surely are not confined to this function. That the marrow also serves as the breeding-place of lymphocytes has been thoroughly established by the researches of Arnold, Neumann, and others, though the conditions here are not nearly so simple.

In the normal lymph-glands we find, at the germ-centers, large lymphocytes ready to divide; round them, large masses of small lymphocytes ("daughter-cells"); and in the lymph-sinus, polymorphonuclear cells.

In the normal marrow we find: (a) Lymphocytes, large and small. (b) Polymorphonuclear neutrophiles of all sizes, some very small; these are chiefly in the marrow-veins. (c) "Myelocytes" or mononuclear neutrophiles; these are the commonest of all varieties in the marrow, and are of all sizes, like the lymphocytes in the lymph-glands. (d) Eosinophiles—mononuclear or polynuclear, and of all sizes. (e) Basophiles, both finely and coarsely granular (γ and δ granulations). (f) Since the young granules have often different staining affinities than the older ones, it is often possible to find, in the marrow, cells containing granules of different tints.

Now, all these varieties may be found outside of the marrow in healthy persons (*e. g.*, in the intestine or peritoneum) except the mononuclear neutrophiles, which accordingly we are right in calling "myelocytes" or marrow-cells, despite the fact that so many other varieties may also be found there. Under pathologic conditions, myelocytes are found outside of the marrow, in the blood, the secondary lesions, and in various organs, and the condition may accordingly be called myelemia or myelocythemia.

So far as any organ can be referred to in connection with one or another type of leukemia, we have (1) the myelogenous cases on the one hand, in which the lesions are chiefly or primarily of the marrow type, or in which the changes in other organs suggest the appearances of the bone-marrow; and on the other (2) the lymphadenoid type, in which the marrow, like the other organs, takes on the appearance of lymphoid tissue, while the spleen and glands show the most marked changes. This, however, does not account for the great enlargement of the spleen in myelogenous cases, which accordingly remains an unexplained fact. It is probably wiser to classify the cases of leukemia by their duration and the nature of their blood changes.

The influence of the factors usually mentioned in discussing the etiology of the disease is so slight, if it exists at all, that it may be dismissed with a word. The number of cases in males is greater than in females; the extremes of infancy and old age are seldom affected. Race, general environment, and the influence of other disease is of no importance. Inheritance may play a part. Transition from pernicious anemia or from Hodgkin's disease to leukemia are said to have occurred, but the writer has never seen such a case nor any satisfactory account of one.

CHRONIC MYELOCYTHEMIA.

The drop, as it exudes from the puncture, is sluggish in its flow, and on close observation has a slightly opaque look; but in none of the cases which the writer has seen has there been any of the chocolate color or whitish appearance mentioned by so many writers. The partially clotted blood is

sometimes of these hues, and it is probable that the postmortem appearances have unduly influenced the descriptions of the living blood.

In early cases the specific gravity is very high, 1070 or even more; later, when anemia supervenes, it may fall as low as 1036.

Coagulation is slow, and there may be a hemorrhagic tendency. The alkalinity is diminished.

Microscopic Appearances.—Red Corpuscles.—Cases seen within six months of the first symptoms usually show no anemia whatever. Their red cells are normal in number, and their hemoglobin is up to par. This may continue for a year or more; and in cases where death is due to some complication (such as apoplexy or pneumonia), there may be no anemia at any time during the disease.

This is important, as many writers still speak of the disease as if it were a variety of anemia; and many clinicians would not consider leukemia possible in the rosy, vigorous patients in whom the writer has repeatedly seen it occur. It is also fatal to the old theory that the disease is due to the transformation of red into white corpuscles, an idea suggested by the fact that in later stages of the disease the constantly increasing white-cell count is accompanied by a gradual diminution of the erythrocytes.

It is true that, as the disease progresses, we find toward its close a marked secondary anemia, especially in prolonged cases where death is due to gradual exhaustion. Diarrhea, ascites, and other complications are often responsible for all or part of this anemia; occasionally the red cells may reach 1,000,000 or even lower before death.

The red cells show in such cases the deformities, altered chemical affinities, and lack of albumin and hemoglobin characteristic of all severe anemias. But perhaps the most interesting point about the red cells in this type of the disease is the presence of large numbers of nucleated red corpuscles, even when no anemia whatever is present. In the early stages of the disease, when the patient feels perfectly well and there is no reduction in the red corpuscles, we often find enormous numbers of nucleated red cells, more than in the severest types of anemia. As the disease progresses and anemia supervenes, the nucleated corpuscles do not increase in number. They are usually present in every microscopic field from the very first. The commonest type is the normoblast, the nucleus frequently being in a condition of karyorrhexis or karyolysis; but megaloblasts and microblasts are also seen.

The presence of these nucleated red cells shows that there is no necessary connection between them and anemia, and also gives us additional evidence of the importance of the bone-marrow in the disease. In lymphemia there is no such appearance of erythroblasts; indeed, they may be entirely absent, and, if present, are proportional to the grade of anemia.

Accepting the theory that this form of leukemia is due to a hyperactivity of cell formation in the bone-marrow, combined with an increased perviousness of the passages through which the cells are ordinarily sent out from the marrow into the blood, it is easy to understand how nucleated red cells might escape into the blood along with the myelocytes and other cells which are normally retained for further development. This certainly seems a plausible explanation of their presence.

Leukocytes.—On the warm stage, ameboid leukocytes are less numerous and less active than is usual or than in leukocytosis, owing to the presence of nonameboid myelocytes.

Quantitative Changes.—In the 38 cases of which the writer has notes, the average count of leukocytes at a comparatively early stage of disease (three to eight months from the first symptoms) was 430,000 per c.mm. The highest count in the series was 1,072,222, and the lowest 98,000. In the late stages they have been found even more numerous than the red corpuscles, but the highest ratio in the writer's series was 1 white to 2 red, the average ratio in 38 cases being 1 : 7 (normal, 1 : 750).

As the disease progresses the number of leukocytes usually rises slowly; but remissions occur, with or without therapeutic influence, in which the count may actually fall to normal, and this may persist for weeks or even months. Further, the count may vary 30,000–50,000 in either direction from day to day without known cause.

The development of an intercurrent infection during the course of leukemia of this type is rarely without some marked effect on the blood. In the great majority of cases the count falls sharply, *e. g.*, from 400,500 to 89,000 (Herrick), from 246,000 to 57,300 (H. F. Müller). The nature of the infection (grip, pneumonia, miliary tuberculosis, erysipelas, etc.) plays no important part; the effect is the same.

Rarely, as in one of Müller's¹ cases, the count may rise considerably—*i. e.*, from 180,000 to 400,000—and there is one case on record in which infection (acute articular rheumatism) produced no effect on the blood (Richter). Goldschneider found that by the injection of splenic extract or other substances he could bring about a diminution of the leukocytes, like that due to acute infections—without, however, bettering the patient's condition.

Qualitative Changes.—Polymorphism.—In normal blood we find the varieties of leukocytes pretty sharply differentiated one from another. Transitional forms are relatively rare, and it is not difficult to determine the relative percentages of the different elements. In the form of leukemia under discussion, the opposite is the case. The first impression we get of the blood is that a classification of the swarms of leukocytes seen is utterly impossible. This impression scarcely ever wears off, and the study of several hundred specimens from 27 cases of this disease leaves the writer still with the feeling that a differential count of the leukocytes with Ehrlich's triacid stain is to a considerable extent arbitrary or even impossible. Between each two of the ordinary types, there are countless transitional forms which it is impossible to classify satisfactorily under any of the recognized types. This point has been much insisted on by Weiss, and is certainly of importance. With an eosin-hematoxylin stain, which blurs several important varieties together, we find the blood less complicated; but the simplicity comes from ignoring instead of solving the difficulties.

Myelocytes.—Nevertheless, certain essential characteristics of the blood stand out very strongly; the most striking and important of these is the large number of "myelocytes" or nonameboid mononuclear neutrophiles.

From 20 to 60 per cent. of all the leukocytes present are to be identified by their single round or oval nucleus and neutrophilic granules, as similar to the common type of marrow-cell and identical with Ehrlich's and Müller's description of "Markzellen." They are of all sizes, from 9 to 23 μ diameter, and seem at first sight to fill up almost the whole field. The nucleus is pale, usually sharply differentiated from the protoplasm, and often

¹ Müller, *Deut. Arch. f. klin. Med.*, 1., 47, 1892.

excentrically placed. Occasionally we catch one of these cells in mitotic division in the circulation, so that two distinct nuclei are seen at the poles of the cell.

Although there are nearly always from 20 to 40 per cent. of typical myelocytes (37 per cent. on the average in the writer's series), yet there are always many cells regarding which it is difficult or impossible to decide whether they are to be classed as myelocytes or not.

It will be remembered that the large lymphocyte differs from the myelocyte only in that the former has a nongranular protoplasm. Now, in leukemia of this type there are always many cells as to the protoplasm of which the conscientious observer feels in doubt. Is it granular or not? It may be diffusely stained of precisely the same violet or pink tint as the neutrophilic granules, and at certain points there are indistinct indications

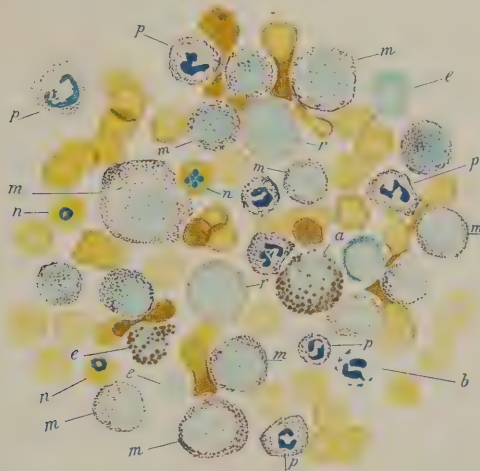


FIG. 160.—Myelogenous leukemia: *a*, eosinophilic myelocytes; *b*, "mast-cell;" *e*, *e*, ordinary eosinophile; *m*, *m*, myelocytes; *n*, *n*, normoblasts; *p*, *p*, polynuclear neutrophiles; *r*, *r*, Reizungsformen (Türk). (Cover-glass film, stained with Ehrlich's "triacid" and drawn with camera lucida.)

of granulation. Under whatever heading we class such cells, we remain dissatisfied with our judgment.

Again, the polymorphonuclear neutrophiles are identical with the myelocytes, except for the shape of the nucleus; but there constantly occur in myelemia cells the nucleus of which is large and pale and excentrically placed, like that of the myelocyte, but which shows at some point an indication of a slight indentation. Shall we class such a cell as polymorphonuclear because of the single slight indentation? If we do, it seems ludicrous to lay so much stress on so small a point. If we do not, the question arises again and again as to how large an indentation a cell nucleus must possess to become "polymorphous," and the decision depends on the personal equation of the observer. We can hardly escape the conviction that there are cells in process of development from large lymphocytes into myelocytes, and from myelocytes into polymorphonuclear cells, which it is entirely impossible to classify accurately.

It is the writer's practice, in the color analysis of myelemic blood, to make

separate headings for cells intermediate between these three varieties, and give up the attempt to force all cells into any of the conventional classes.

Lymphocytes.—Cells of this type are relatively few, usually less than 6 per cent., but absolutely they are often greatly increased. The large type is more common than the small, and shows, as above noted, a tendency toward dark-purple protoplasm—darker than the nucleus, such as is not seen in normal blood, although occasionally met with in the anemias of infancy and in infectious diseases (Türk's "Reizungsformen").

Polymorphonuclear Neutrophiles.—As already mentioned, the percentage of these cells depends considerably upon the personal equation of the observer. Their small size is striking, many being under $10\ \mu$ in diameter, with intensely staining nuclei. Such forms are frequent in the normal marrow. Of the forms approximating to the myelocytic type, enough has already been said. The average percentage in the writer's cases was 49.2—*i. e.*, less than normal; but absolutely they are enormously increased, even to 70 times their normal number.

Eosinophiles.—Ehrlich's original statement regarding the presence of these cells in leukemia was that they were always *absolutely* increased. This is true, but not characteristic of the disease. Their percentage is usually about normal, occasionally somewhat increased. The striking point about them is not their excessive number, but their variations from the type seen in normal blood. Normally eosinophiles are about the size of the polymorphonuclear neutrophiles, and their nuclei are also polymorphous and very loosely connected to a mass of granules, the outline of the cell being more irregular than that of any other form of leukocyte. Now, in leukemia, one finds, to be sure, this ordinary type of eosinophile; but also much larger mononuclear eosinophiles, to which Müller and Riedel called attention under the name of "eosinophilic myelocytes." The cell is not scraggy or loosely constructed, as ordinary eosinophiles are; it is round and compact, usually larger than any normal leukocyte, and its nucleus in all ways resembles that of the ordinary (neutrophilic) myelocyte, from which it differs only by the possession of eosinophilic granules.

Dwarf forms no larger than red cells are also seen, sometimes with one nucleus, sometimes polynuclear.

Basophiles.—Almost all cases of myelocythemia show from 2 to 6 per cent. of basophiles (*i. e.*, from 3000 to 140,000 per c.mm.), usually with trilobed nucleus (though mononuclear forms are also seen), and coarse basophilic granules staining with methylene-blue or dahlia, and crowded together at the outer edge of the protoplasm. They are very irregular in size and shape, and at times one can only see light spots and streaks in a solid basophile border. These cells are probably identical with the "mast-cells" of the alimentary canal and of connective tissue in general. Mention has been made above of the fine (δ) granules of basophile affinity in the protoplasm of large lymphocytes; these are not to be confounded with "mast-cell" (coarse) granulations.

Irregular Forms.—Mention has already been made of the forms transitional, in appearance at any rate, between myelocytes and polymorphonuclear neutrophiles and between myelocytes and lymphocytes. Besides these, we find occasionally in leukemic blood: Nongranular polymorphonuclear cells, the protoplasm entirely unstainable or diffusely basophilic; cells of the size of the smallest lymphocytes, with neutrophilic granules; cells with two sets

of granules—*e. g.*, neutrophilic and eosinophilic, neutrophilic and basophilic, eosinophilic and basophilic—these are rare, but do occur; cells of various sizes, the peculiarity of which is in possessing not over ten granules of one or another kind, sprinkled very sparsely through their protoplasm, with wide intervals between.

Changes in the Other Tissues.—The Spleen.—The organ is tremendously enlarged and not infrequently is over a foot long, with corresponding increase of breadth and thickness, and a weight of 15 pounds is not unusual. The size of the organ in most cases gradually increases during the first two-thirds of the course of the disease, and then remains about stationary. In some cases, however, great alterations in size may occur—sudden increase from hemorrhage into the organ, sudden or slow decrease from diarrhea, intercurrent infections, or therapeutic influence. Rupture may occur spontaneously or from traumatism. The notches on the upper border—one, two, or three in number—are notable. Adhesions to neighboring organs and patches of perisplenitis are common.

The consistency is greatly increased, chiefly owing to the growth of stroma. The capsule is thickened and its surface is often coated with the results of old or recent perisplenitis in patches or diffusely, and in the stroma deposits of lime salts may occur. The section surface is, on the whole, paler and drier than normal, often mottled or marbled with brown and yellow patches on a reddish-gray background, and scarred with islands of connective tissue marking the areas of old hemorrhagic infarction. Earlier stages of the same process may be seen in other parts of the organs—red, brown, or yellow, according to the age of the lesion. The overgrowth of follicles and stroma compresses the pulp, so that fatty degeneration and atrophy result, leaving considerable quantities of pigment granules, free or enclosed in cells and surrounded by fibrous tissue. In some cases the hyperplastic Malpighian follicles stand out as grayish nodules, lobulated clusters, or beaded strings. The trabeculæ are plainly seen, forming a white network across the cut surface.

Microscopically we find the increase of connective tissue very striking, except in early cases—the reticulum is thickened and often forms large scars. The Malpighian bodies are scarce. The bulk of the cells in the follicles are lymphocytes of various sizes, the small type being most numerous; but in contrast with the normal spleen, “in which the lymphocytes are the overwhelmingly predominant element,” the leukemic spleen contains remarkably few lymphocytes. Myelocytes are also numerous, though not as numerous as in the blood. Polymorphonuclear neutrophiles, eosinophiles, and mast-cells are likewise plentiful. The outlines of the follicles are usually lost in a confluence of lymphoid tissue, which sometimes accumulates into genuine lymphomas—which do not, however, consist wholly of lymphocytes, as in the lymphomas of chronic lymphemia, but contain many of the other blood and marrow elements. The number of mitoses is small. Hindenburg has observed mitosis in eosinophiles of the spleen. Myeloplaxes are also to be seen, containing débris of various kinds. Nucleated red cells are numerous and intimately mixed with the leukemic collections.

Owing to the presence of eosinophiles in the organs, Charcot-Leyden crystals can be found in the tissues, especially if the latter are left several days exposed to the air before examination. Leucin, tyrosin, xanthin, and substances allied to peptone, have been detected in the spleen by chemical analysis.

The Liver.—Considerable enlargement is present in almost every case, varying from time to time from the same causes that affect the size of the spleen. The organ may weigh 20 pounds. The enlargement is usually symmetric, but, as in other forms of enlargement, it may affect more especially the right lobe. The capsule is usually smooth or shows small patches of thickening. The consistency is increased.

The appearance of the cut surface is influenced by three elements: Stasis, fatty change (degenerative or infiltrating), and leukemic infiltration. The combinations of these processes with areas of relatively normal tissue give rise to a great variety of appearances. In general, we have a mottling of gray, yellow, and dark red, the distribution of the colors depending on the combination of pathologic processes present in the particular case.

The stasis brings about dilatation of the liver-capillaries, to which the leukemic blood brings enormous numbers of leukocytes; the centers of the acini undergo a pressure atrophy, so that the space occupied by the leukocyte-stuffed capillaries is very large.

Fatty changes in consequence of pressure or disturbed metabolism are common in advanced cases.

The true leukemic infiltration presses into the lobules from without inward, *i. e.*, from the peripheral zone toward the center. It may be diffuse or in nodular masses (lymphomas), but the origin from the periportal region can usually be made out.

Microscopically we find the leukemic infiltrations to consist of cells like those in the blood. In the dilated capillaries are large numbers of myelocytes. The lymphomas contain lymphocytes and polymorphonuclear cells with relatively few myelocytes. Eosinophiles are also very plentiful. Plasma-cells and endothelial cells are common.

The most striking and important point about the histologic changes is the enormous number of mitoses in the dilated capillaries. Nowhere else are they so numerous, not even in the germ-centers of lymphoid organs. The only other place in which Hindenburg found them so numerous was in the lymph-channels of the lymph-glands. The lymphocytes and myelocytes are the cells in which most of the mitoses occur.

Glisson's capsule is often infiltrated with lymphocytes and polynuclear neutrophiles. Large phagocytic giant cells, presumably of the leukocyte type, are numerous in the dilated capillaries; and within these cells, or outside of them, a good deal of nuclear debris and pigment is seen.

The same chemical substances mentioned in connection with the spleen have been found in the liver.

The Bone-marrow.—The fat and bone-spicules are largely atrophied, so that large pieces can be cut without previous decalcification. In place of these elements we find a great increase in the marrow-cells, both white and red. Sometimes the increase of red cells predominates, and then we get the so-called lymphoid or currant-jelly marrow; this is usually in long-standing, anemic cases. If the colorless corpuscles are especially increased, we see the "pyoid" or grayish-yellow marrow. Neither condition is at all characteristic of leukemia. Actual hemorrhages or circumscribed nodular masses are occasionally found. All the cells of the normal marrow are present in increased numbers, but the "myelocytes" (neutrophilic, with round or oval nuclei) are the most numerous, while polynuclear neutrophiles come next in frequency. The Charcot-Leyden crystals, upon which so much stress has

been laid, have been recently shown to be connected with the degeneration of eosinophiles, and can therefore be found in any tissues containing these elements after exposure to the air. They have, of course, no diagnostic value.

Lymphatic Glands.—As a rule, slight enlargement is found in all of the normal gland-chains (axillary, inguinal, bronchial, mesenteric, etc.), the enlargement being due, according to Taylor, not to lymphocytes, but to adventitious cells—myelocytes, polynuclear neutrophiles, eosinophiles, and mast-cells. These strangers compress and almost obliterate the germ-centers. Mitoses are few, and cell-degenerations frequent.

Secondary Effects of the Disease.—The pressure of the enlarged spleen and liver may give rise to ascites, enteritis, or intestinal obstruction. The spleen and liver push up the diaphragm, displacing the heart and embarrassing its action.

Metastatic Nodules.—An account of the metastases which occur rarely in this type of leukemia will be given more fully under Chronic Lymphemia, in which they are the rule. The same elements are present in the metastases which we have described in the leukemic infiltrations of the liver and spleen, namely, all the marrow-leukocytes.

Leukemic Priapism.—Various explanations of this symptom have been advanced. Pressure on the nerves or veins concerned in erection may explain certain cases. Thrombosis of the corpora cavernosa has been found in some cases, but it is doubted by some writers whether this can explain the condition.

In a case recently recorded by Kast, in which the priapism lasted till death, the corpora cavernosa were found stuffed with lymphoid tissue, while the spongy bodies consisted of tough masses of connective tissue.

Chloroma.—Occasionally and for reasons unknown, the lesions take on a greenish color, to which the name of chloroma has been applied.

Hemorrhages.—Although less diffused and less prominent than in acute cases, hemorrhages may lead to death, as by apoplexy or loss of blood in epistaxis or metrorrhagia. In a case under the writer's observation, deafness came on, due to hemorrhage into the middle ear. Hemorrhages into the spleen and marrow have been mentioned.

CHRONIC LYMPHEMIA.

Fränkel's denial (in 1895) of the existence of this condition has caused a number of observers to bring forward cases in refutation of his assertion and increased our knowledge of the disease. Cases have been recorded by Grawitz, Wertheim, Weiss, Herrick, Dock, Marischler, Hindenburg, Benda, and others. The writer has seen six typical cases. Fränkel has lately retracted his assertions.

The Blood.—**Red Corpuscles.**—In striking contrast to myelogenous leukemia, we find in chronic lymphemia an absence of nucleated red corpuscles, except in extreme cases in which the anemia has become intense. The number of corpuscles is usually reduced considerably, more than in average cases of myelogenous leukemia. Counts over 3,000,000 are seldom obtained; but in one case which the writer has followed for over three years, the red cells are always over 5,000,000. There is nothing special to be said of the finer changes of the erythrocytes, which are those already described under Secondary Anemia.

White Corpuscles.—The number may be as great as in any form of leukemia. For instance, Dock's case showed 580,000 at the time of death. One of the writer's cases had, six months ago, 1,480,000 leukocytes to the cubic millimeter; this patient is still alive. The majority of cases show, however, lower counts than the average in myelogenous cases. The other cases of the writer had from 80,000 to 25,000, and this is about what we expect to find. One subacute case had, six weeks before death, 132,000 leukocytes per cubic millimeter.

Color analysis shows that practically all the white corpuscles present are of the small lymphocyte type—over 99 per cent. in Dock's case, 99.9 per cent. in one of the writer's, 98.6 per cent. in another. These lymphocytes correspond in all respects to those of normal blood; that is, they may have light or dark nuclei, visible or invisible protoplasm; their nucleus is generally round, occasionally indented, rarely double. The small remnant of leukocytes other than lymphocytes may be made up of any of the other varieties—*i. e.*, of eosinophiles, myelocytes, or polynuclear neutrophils. Thus, in Dock's case the eosinophiles were about 1 to every 2000 lymphocytes; the myelocytes 1 : 5000. In one of the writer's cases, there was at first 1 polymorphonuclear neutrophile for every 1000 lymphocytes, with no other varieties at all. Later, eosinophiles and myelocytes in very small numbers became visible. The excess of lymphocytes is not always so extreme, however. Another of the writer's cases showed, among the 80,000 leukocytes per c.mm., the following: Polymorphonuclear neutrophils, 17.2 per cent.; small lymphocytes, 80.5 per cent.; large lymphocytes, 2.1 per cent.; eosinophiles, 0 per cent.; myelocytes, 0.2 per cent.

The contrast of chronic lymphemia and chronic myelocythemia is as sharp as possible: in the first, an endless monotonous expanse of lymphocytes, all pretty much alike; in the second, every possible type of leukocyte, granular and nongranular.

Changes in the Blood-making Organs.—**The Spleen.**—As a rule, the enlargement is moderate; the organ projects one or two fingers' breadth below the costal margin, and is perhaps seven to nine inches in length. But occasionally the enlargement is as great as in any form of leukemia. In Dock's case the organ reached from the eighth rib in the axillary line to the left iliac fossa and across to the middle of the left rectus muscle. In a case which the writer has recently seen, the spleen was even larger, extending decidedly to the right of the navel. In view of these facts, it is entirely improper to speak of "splenomyelogenous" leukemia, since both spleen and marrow (see page 490) may be equally affected in lymphemia.

The other characteristics of the spleen (as regards density, color, etc.) are the same as those already described in the myelogenous form of the disease. The greatest difference is, however, seen when we come to the microscopic appearances.

Microscopic Appearances.—The bulk of the cellular constituents, like those of the blood, is made up of small lymphocytes; whereas in acute lymphemia the prevailing type of cell is that commonly seen at the germinal centers of lymphoid follicles, and the surrounding zone of small dark daughter-cells is much reduced or gone, in chronic lymphemia the small dark lymphocytes have everything their own way, and the larger and paler mother-lymphocytes are much less in evidence. In the spleen we may have

a diffuse increase in the number of the normal follicles or definite lymphomas forming solid grayish nodules made up almost entirely of lymphocytes. As in the acute lymphemias, the distinction of germ-center and boundary zone is wiped out.

The Liver.—As a rule, the organ is not greatly enlarged; but now and then it reaches to the navel. The leukemic process in it is usually confined to metastatic lymphomas, which stand out strikingly as grayish nodules on the dark-red section-surface and may be seen beneath the capsule. Occasionally we find diffuse infiltration of the whole liver-substance, with numberless mitoses in the capillaries, with or without circumscribed lymphomas.

Lymphatic Glands.—Any or all of the visible lymphatic glands may be enlarged. Masses in the neck, axillary, and groins are notable, but seldom attain the size seen in Hodgkin's disease. The mesenteric, retroperitoneal, and bronchial glands, the lymphoid tissue of the mouth, throat, and gastro-enteric tract, are often affected. The structure of these glands is that already described in the case of the spleen; masses of small lymphocytes make up the whole of it.

Metastatic Nodules.—The number of metastatic lymphomas is greater and the distribution more widespread than in any other form of leukemia. The serous membranes (pleura, peritoneum, pericardium, etc.), all the mucous membranes, the skin, the organs of special sense, the brain and meninges, the heart, lungs, kidneys, pancreas, and sexual organs may any or all of them be affected. The metastases appear as grayish, circumscribed nodules, not different in appearance from metastatic sarcomas; but microscopically they are made up wholly of masses of small lymphocytes, arranged as in the organs before described. Metastases in the bone-marrow often occur, and the marrow is almost always hypertrophied, and evidently takes an important part in the process; but the hypertrophy is not of the normal marrow-elements, which are crowded out and almost abolished by the lymphocytic infiltration. The usual marrow-elements (eosinophiles, nucleated red cells, neutrophiles, and basophiles) are therefore greatly diminished in the marrow, as well as in the blood.

ACUTE LYMPHEMIA.

Etiology.—Most cases occur between the ages of eleven and twenty-four. Males slightly predominate. Many points about the disease suggest an acute infection, and it has been maintained that the lesions so frequently found in various parts of the alimentary tract might give entrance to micro-organisms. Abrastow reports two cases which strongly suggest contagion. But no positive evidence on these points has yet been presented.

The Blood.—The blood of truly acute cases—that is, of cases where the acute symptoms and speedy course to death within a few weeks is not simply the end-stage of a chronic leukemia—is usually of a definitely different type from that of other varieties of leukemia. It is almost always a lymphemia; for, while not all lymphemias are acute, almost all acute cases are lymphemic—that is, the blood-leukocytes correspond rather to those found normally in the lymphadenoid apparatus than to those predominating in the marrow. But the blood shows in the great majority of cases a different state of things from that already described under Chronic Lymphemia. We will begin with the point of greatest interest, namely, the leukocytes.

Leukocytes.—As a rule, the total count of leukocytes is smaller than

that of any other form of leukemia. From 30,000 to 70,000 per c.cm. is the ordinary count. As in other forms of leukemia, the number varies greatly from time to time, and is usually much decreased during the course of any intercurrent infection (sepsis, pneumonia, etc.). It may possibly be affected by treatment, but this is more than doubtful.

The following table illustrates the effect of an intercurrent septicemia on the count, in a case watched by the writer. The diminution of the number was associated with a great increase of degenerating forms in the blood.

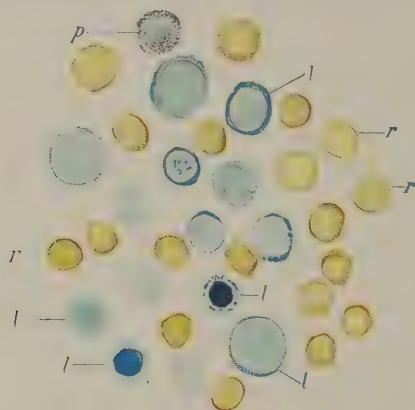


FIG. 161.—Lymphatic leukemia: *l, l, l*, lymphocytes; *p*, polynuclear neutrophile; *r, r*, red cells.

Date.	Leukocytes per c.mm.	Percentage of lymphocytes (large and small).
April 3	31,600	96.5 per cent.
" 4	31,000	
" 6	28,505	93.6 per cent.
" 8	44,000	
" 10	31,000	95.5 per cent.
" 12	40,000	
" 13	Sepsis began.	
" 20	5,661	
" 21	4,000	
" 22	3,400	92.0 per cent.
" 24	3,200	
" 28	800	
" 29	471 †	94.7 per cent.
Death on 29th.		

As indicated in this table, the percentage of lymphocytes is very high, not markedly different from that of chronic lymphemia. It remains so, as a rule, despite the influence of the intercurrent affection on the total count; in other words, this intercurrent complication does not change the method in which the cells are produced. But, though the percentages remain the same, there is a change in the appearance of the cells, which probably explains the diminution in the total count. This change consists in the increase of degenerative forms, until sometimes hardly a sound leukocyte is to be seen. This leads us to suppose that a wholesale cell-destruction is taking place under the influence of the complicating infection. The supposition is

strengthened by the fact that the spleen and lymph-glands grow smaller and softer at the same time and show microscopically evidence of extensive cell-destruction; the simultaneous increase in the uric acid excreted in the urine is another evidence of cell-destruction.

But although the percentage of lymphocytes is about the same as in chronic cases, we find that the increase of lymphocytes is made up chiefly of large and medium-sized pale forms, and not exclusively of the small dark forms characteristic of chronic lymphemia. The subacute cases show a preponderance of a type of lymphocyte intermediate between the smallest and the largest. In general, although no line can be drawn between chronic, subacute, and acute cases, we can say that, as a rule, the more acute the case, the larger the lymphocytes.

The large lymphocytes of acute leukemia correspond exactly in many instances with those of normal blood. The great majority contain a large nucleus, with but faint affinity for coloring matters of any kind. This nucleus is often indented or even double. What is more peculiar to this disease is the relatively large number of lymphocytes showing evidence of division; in some instances, such cells are very common. Another feature is the frequency of signs of degeneration in the large lymphocytes. Even in normal blood, this form of leukocyte is especially apt to show degenerative changes; but in some cases of acute leukemia these changes are seen in almost every cell. All forms of leukocytolysis, according to the elaborate researches of Botkin,¹ can be studied in acute leukemia, especially when some intercurrent infection takes place.

(a) The whole leukocyte may swell symmetrically, the nucleus becoming vacuolated and fading indistinguishably into the surrounding protoplasm, which stains more intensely than the nucleus.

(b) The nucleus may remain relatively unaffected in size and staining reaction, while the protoplasm disappears altogether or is seen only in tattered fragments around the nucleus.

(c) The whole cell may swell as in the first type (a), the protoplasm being unstained except at its outer rim.

Combinations of these types are also to be seen; Litten has noticed fatty degeneration of the leukocytes.

As mentioned above, the lymphocytes of acute leukemia may show two nuclei; but they do not remind us at all of the polymorphonuclear neutrophils, (a) because they never contain neutrophilic granules, (b) because their nuclei are well separated, pale, and round or oval, never twisted or fragmented, like true polymorphous nuclei, (c) because of the frequent presence of fine basophilic granulations in their protoplasm.

The dividing or divided forms are much less common in the peripheral capillaries than in those of the internal organs (*e. g.*, lungs, liver, kidneys), where they are very abundant (Fränkel). All that is needed to make the leukocytes divide in this disease is a slowing of the circulation. The special conditions of the blood-making organs are helpful, but not essential.

Fränkel saw no ameboid movements whatever in these lymphocytes, and this is also the writer's experience.

As stated above, all other varieties of leukocytes—polymorphonuclear neutrophils, eosinophils, and myelocytes—generally disappear from the blood, but occasionally a few of each of these varieties are seen.

¹ *Virchow's Archiv*, cxlv., 1896.

Red Corpuscles.—The red cells are usually much more reduced than in chronic cases, not infrequently falling nearly to one million before death. The usual deformities of severe anemia are seen. Regarding nucleated red corpuscles, the blood stands midway between that of chronic myelogenous leukemia, in which the number of erythroblasts is very great, and chronic lymphemia (chronic lymphatic leukemia), in which they are very scanty or altogether absent. The number approaches that seen in severe secondary anemia—which is, in fact, present in this form of the disease. Normoblasts form the great majority of the erythroblasts found, but megaloblasts also appear occasionally. Cases occurring in children form an exception to this rule; in them, nucleated red cells are usually very abundant, as is the case in nearly all severe diseases affecting the blood of infants.

Fränkel noticed an enormous accumulation of uric acid in the blood, 22 mgr. in 100 c.c.

Postmortem Appearances.—The color of the blood is rarely noteworthy in acute cases, unless extensive coagulation has taken place; that is, in autopsies performed immediately after death, the color of the blood is not usually such as to attract attention. The most striking feature macroscopically is the presence of countless hemorrhages in the skin, in all mucous and serous surfaces, and in the organs themselves. Hemorrhages may occur in the brain or subdural space. In the internal ear, the mouth, gums, esophagus, larynx, stomach, intestine, pleura, peritoneum, bladder, vagina—in all the internal organs, the pelvis of the kidney, and in numberless other situations—hemorrhages of varying amount may be seen. They are useful as guides; for wherever we find hemorrhages, we are sure to find lymphomas, either macroscopic or microscopic.

The alterations of the lymphadenoid apparatus divide themselves as follows: (a) Those in the normally visible lymph-glands, including those of the whole gastro-enteric tract; (b) those in the spleen and bone-marrow; (c) metastatic lymphomas.

Visible Lymph-glands.—The adenoid tissue is transformed into soft whitish or grayish-red tumors, the cut surface of which is sprinkled with spots of hemorrhage. The glands are not greatly enlarged, compared with those seen in chronic lymphemia or in Hodgkin's disease; for they are seldom larger than a walnut, and usually smaller. "The characteristic point about them is their thoroughly atypical, nonregional distribution" (Benda). One meets, for example, with a combination of axillary and mesenteric enlargement, such as is seen in no other acute disease, unless it be secondary syphilis. Occasionally the disease may be confined to the alimentary canal and bone-marrow; the spleen, axillary, inguinal, mesenteric, and bronchial glands remaining normal.

Spleen and Bone-marrow.—The spleen is nearly always symmetrically enlarged, although not nearly to the extent seen in chronic lymphemia or chronic myelogenous leukemia. One rarely sees a spleen over eight inches long, with corresponding thickness and breadth. It is usually softer than normal, contrasting in this respect with the firm, tough spleen of chronic cases. There is a lack of distinction between pulp and follicles. An elastic but not fluid mass projects between the trabeculæ and vessels. The section surface is of a uniform grayish-red color.

The bone-marrow always shows some alterations, but their extent varies greatly in individual instances. We may have (a) spots of red lymphoid

marrow, or hemorrhages into the marrow; (*b*) large tracts of red marrow, as, *e. g.*, one-half the femur or more; (*c*) homogeneous, grayish-red or "pyoid" marrow, with here and there yellow-greenish portions; (*d*) discrete, pale, grayish-white nodules scattered here and there (these are much more common in chronic cases).

"In a general way, the gross appearances of the marrow stand midway between those of pernicious anemia and those of chronic leukemia, but approximate more nearly to the first" (Benda).

Metastatic lymphomas are always numerous, far more so microscopically than the gross appearances suggest. In acute cases they are usually very small, and are visible to the naked eye only when aggregated in large numbers or confluent. As has been stated, they are to be found wherever we find hemorrhages. But many light areas, which macroscopically appear to be lymphomas, turn out to be something else: *e. g.*, in the liver, fatty changes; in the kidney, embolic abscesses. These conditions may exist side by side with genuine lymphomas.

There is no organ in which the lymphomas may not be found. Benda mentions the following list: The myocardium, pericardium and endocardium, the pleura (extending in one case to the lung), liver, kidney, renal pelvis, ureter, and prostate, in the meninges, brain, pons, and infiltrating the cerebral nerves. The ulcerations of the mouth and gums, which form so prominent a clinical feature, are usually dependent on lymphomatous metastases there. The larynx is also often involved, at times to such an extent that symptoms of suffocation, necessitating tracheotomy, appear.

In Askanazy's case, the whole alimentary tract was studded with accumulations of lymphoid tissue, the solitary follicles and Peyer's patches being everywhere enlarged and partly ulcerating, and the stomach showing ing erosions and hemorrhages due to lymphoid infiltration and pressure necrosis.

In a recent case of Fränkel's, the facial nerve was infiltrated with lymphocytes, which extended between the fibers of the nerve itself. Similar changes were found in the acoustic nerve and in the vagus. During life these lesions caused facial paralysis, deafness, and palpitation. The writer has seen an eyelid infiltrated and greatly thickened by similar growths, and the eye pushed forward by a growth in its rear.

Large-sized lymphomas, such as are common in chronic lymphemia, do not usually form in acute cases, perhaps for lack of time.

Microscopic Appearances.—In many cases the same elements occur in all the lesions, no matter in what organ or on what surface they are planted. Occasionally there is a difference between the marrow changes on the one hand, and those of the gland-tumors and metastatic nodes on the other.

The greater part of the gland-tumors is made up of cells corresponding exactly to those previously described as "large lymphocytes" (Ehrlich's large mononuclear elements, Löwit's "Leukoblasts," Müller's "Theilungs-reife Zellen," Benda's "Lymphogonien"); that is, they are cells of about 12 μ diameter, containing a pale-staining, finely reticulated nucleus, usually round or kidney-shaped, and surrounded by a varying amount of protoplasm, which is either free from granules or contains very fine, closely packed basophilic granules, and which itself has a faint affinity both for acid and basic stains, or remains entirely unstained. In the normal lymph-

gland these cells divide to form the ordinary small lymphocytes of the blood and lymph, this division taking place in the "germ-centers," around which the "daughter-cells" (small lymphocytes) are arranged in large numbers, so that they appear to make up most of the gland substance.

In acute lymphemia, it is still these cells in which most of the mitoses are found; but germ-centers there are none. All distinction of germ-centers and sinuses is lost, and only the large central sinus and the lymph-vessels leading from it can be made out. There is seen a small number of small lymphocytes scattered singly or in clumps among the large lymphocytes; but in these small forms the number of mitoses is relatively slight, and the total effect of the section is that the small cells have been largely replaced by large ones.

The spleen and metastatic nodules show similar appearances, but in the spleen the excess of large over small lymphocytes is less striking than in the lymph-glands, and hemorrhages are more abundant. There is good reason to suppose that metastases are due to a "colonizing" activity on the part of the cells of the circulating blood.

When metastases occur in the mucous membrane of the alimentary canal, we find in the deeper layers the usual abundance of "mastzellen," and in the superficial layers near the surface polynuclear cells. This corresponds to the normal arrangement of the leukocytes of the alimentary canal, on which the cell system of the metastatic lymphomas is grafted.

Microscopically the marrow shows, of course, the same wide variations in individual cases that have been alluded to in its gross appearances. In the cases showing macroscopically nothing but a greater or less amount of red marrow instead of fatty marrow, the microscope shows principally nucleated red cells mixed with eosinophiles and small myelocytes. In the more pyoid cases there are found chiefly large mononuclear cells exactly like those in the lymph-glands, but possessing, many of them, neutrophilic or basophilic granulations. In such cases eosinophiles, erythroblasts, and polymorphonuclear cells are rare. The main type of cell is, even in the marrow, the lymphocyte.

In the lungs Taylor found the infiltrations around the branches of the pulmonary vessels, around the bronchi and alveoli, and beneath the pleura—*i. e.* in the situations where lymph-nodes are normally found. In the bronchi no lymphocytes were seen.

The changes present in acute leukemia, then, amount only to an intensely vigorous growth of the normal cells of the whole lymphadenoid apparatus and bone-marrow, and are thereby distinctly different from chronic lymphemia, which consists wholly of a heaping-up of small lymphocytes in neoplastic form; different also from chronic myelogenous leukemia, where the marrow elements are those chiefly affected. Yet the glandular tumors of acute leukemia are not entirely unlike those of chronic lymphemia, and the marrow changes may resemble those of chronic myelogenous leukemia. So far, no one has reported any metastatic myelomas, or tumors containing indubitable marrow elements (such as are seen in myelogenous leukemia), in the truly acute cases.

Sections through blood-clot can hardly be distinguished from those through the enlarged glands, showing the apparently complete identity of the cells in the blood with those of the organs; and further, examples of every variety of cells found in the organs occur in the blood. However,

a larger proportion of the large lymphocytes in the bone-marrow show neutrophile granules (myelocytes) than in the blood.

The absence or great diminution of polymorphonuclear neutrophiles in the blood is matched by their great diminution in those limited portions of the blood-making organs in which they are chiefly found under normal conditions—viz., in the marrow-veins and in the lymph-sinuses.

As in other varieties of leukemia, the succession of events is probably this : (1) Action of an unknown stimulus on the blood-making organs ; (2) proliferation of leukocytes in the blood-organs (continued to a greater or less extent in the blood) ; (3) the discharge of these leukocytes into the blood before their normal metamorphosis is finished ; (4) "colonization" of these blood-leukocytes as metastatic nodules.

Where abscesses occur, as in the kidney (*vide supra*), we find them filled, as usual, with polymorphonuclear neutrophiles. This is hard to explain on the usual theory of emigration from the blood, since the blood in such cases contains hardly any neutrophiles. Benda supposes that the lymphocytes of the neighboring metastatic nodules are transformed *in situ* into polymorphonuclear cells—a supposition which seems to the writer very unlikely.

It has been observed by various authors that the effect of an intercurrent infection (septic or other) is not simply to diminish the number of leukocytes (*vide supra*), but often to cause a considerable shrinkage of the tumefied organs, similar to the retrograde changes in sarcomas under the influence of a complicating erysipelas. This is apparently due to cell death, as there is every evidence of cell destruction in the blood and organs of such cases, and the uric acid becomes enormously increased in the urine—an indication that great numbers of nuclei have perished.

In some chronic myelogenous cases there is, as above stated (page 488), an increase and not a diminution of the leukocyte-count, under the influence of infectious complications ; but in acute leukemias this is apparently not the case.¹

Summary.—Leukemia appears under three principal types : Chronic myelocythemia, chronic lymphemia, acute lymphemia.

The first type is characterized by a very large spleen and liver, in which, as well as in the blood and marrow, the marrow types of cells are found. Stages of leukocyte structure intermediate between those seen in normal blood are here present in the blood and organs, giving a very "polymorphous" appearance to them. The characteristic marrow-cell, or mononuclear neutrophile, forms nearly one-half the cellular elements in the blood and organs. The lymphatic tissue, outside of the spleen and marrow, is but little affected.

In chronic lymphemia the blood and organs are flooded with small lymphocytes, the other types of leukocytes being so far reduced as to be hardly noticeable. Large metastatic lymphomas are scattered through the whole organism. The spleen and marrow may be as much affected as in myelocythemia ; but the type of cell found prevailing is entirely different, and the peculiar marrow elements are replaced by small-cell lymphoid tissue.

In acute lymphemia, hemorrhages and ulcerations are prominent. The blood and the blood-making tissues contain great numbers of large pale lymphocytes, like those of the germ-centers of normal lymphoid tissue. Metastatic lymphomas are very numerous, but are generally mostly microscopic in size. No marrow elements are found in the blood or organs,

¹ Except at the time of death.

although in the marrow itself they are less decreased than in chronic lymphemia. The blood-vessels themselves are invaded and ruptured by leukemic infiltration; hence the acuteness of the disease and the frequent hemorrhages.

HODGKIN'S DISEASE.

There is little to be said of this disease which has not already been said of leukemia. Our ignorance of its etiology is of the same degree, its pathology is identical with that of chronic leukemia, and its blood condition is wonderful only in being so entirely normal.

Two points especially deserve discussion: (*a*) Is it a separate disease at all? (*b*) Why is the blood normal (the organ changes being identical with those of leukemia)?

There is little doubt that many cases considered as Hodgkin's disease have been in reality cases of tuberculous or syphilitic adenitis. Only the most careful study can at times distinguish these diseases from Hodgkin's disease. The diagnosis can therefore never be made with certainty during life, and it has been asserted by various writers that what we call Hodgkin's disease is really a congeries of cases, some tuberculous, some syphilitic, some malignant disease, some early leukemia, and some chronic malaria. The distinction between the disease and the various forms of sarcoma of the lymph-glands cannot be made either during life or by the microscope, as there are no reliable differences in cell structure. This haziness is mirrored in the various names given to the affection: Lymphadenoma, lymphosarcoma, lymphoma, malignant lymphoma, pseudoleukemia, splenic anemia, etc.

If the disease is simply an hypertrophy of adenoid tissue without known cause, we cannot well limit the name to the hypertrophy of any one set of adenoid organs, and must admit pure splenic or myelogenous types, as has been done by most German authorities. But this leads to difficulties and even absurdities.

Where a large number of glands is affected, where the course is slow and creeping, and tuberculosis and syphilis can be excluded with reasonable certainty, the diagnosis of Hodgkin's disease seems a natural one. But when only a few glands, only the spleen, or only the marrow is found hypertrophied, we may well feel that the name is little more than a cloak for our ignorance.

Many French writers insist on regarding it as a preleukemic stage of leukemia, basing their theory on a few cases recorded many years ago, in which a transition to true leukemia is said to have occurred. The writer has never been satisfied with the evidence that such cases exist; at any rate, they must be exceedingly rare. It is more likely that the leukocytosis which often appears in the later stages of the disease was mistaken for leukemia, owing to the absence of accurate methods of blood examination.

On the whole, we must regard the question of the nature of the disease and its relations to sarcoma as wholly unsettled, but there is no reason for supposing that it has any close relationship to syphilis or tuberculosis. The existence of pure myelogenous cases is not yet satisfactorily established. Splenic enlargement without symptoms should not, the writer believes, be classed as Hodgkin's disease.

On the question of the relationship of the disease to leukemia, the researches of Benda have recently thrown some light. In leukemia, something occurs which sets free in the blood-current the masses of leukocytes,

produced in the organs equally in leukemia and in Hodgkin's disease. What is this "something"?

Troje assumes a riddling of the septa which normally divide the germ-centers from the lymph-channels, and of the marrow-veins. Benda adds to this hypothesis the fact that he has observed, in leukemic cases, extensive changes in the vessels. Both in the primary growths and in the metastatic nodules he finds the vessel-walls invaded with lymphoid tissue, so that the leukocytes can easily burst through into the vessels. Frequently the elastic layer and the intima up to the very endothelium are riddled with lymphoid growths, and in the larger veins he finds lymphomas projecting into the lumen of the vessel and covered only by endothelium. In Taylor's cases the endothelium was ruptured. The protection afforded to the organism by thrombosis, when, in diseases like tuberculosis, carcinoma, or syphilis, the vessels are invaded, is wanting in leukemia. For some reason, vessels invaded by lymphomas do not become the seat of thrombosis, perhaps because the cells of the lymphoma are such near relatives of those of the blood and excite no reactive hostility, while the products of tuberculosis or cancer, being more foreign to the blood, induce thrombosis.

Benda's observations do not, of course, explain why the lymphomas of Hodgkin's disease do not invade the vessels; but, according to him, they do not do so.

The Blood.—As a rule, there are no changes in the blood, except a progressive anemia of the secondary type, seen chiefly toward the close of the disease and often accompanied by more or less polymorphonuclear leukocytosis. Sometimes this is obviously dependent on suppurations in the enlarged glands; in other cases, its origin is not clear. During the greater part of the course of most cases, the leukocyte-count is normal, with often a slight lymphocytosis.

Lymphadenoid Organs.—The cervical glands are those earliest involved; later, the intrathoracic, axillary, inguinal, and mesenteric glands. The growths in the neck may be as large as a child's head. They are soft, movable, and discrete in the earlier stages, becoming harder and more matted to each other and to the skin in the later stages. Usually the disease remains limited by the capsule of the glands, but it may pierce through and proliferate outside of it. Softening and suppuration occur but rarely.

The spleen may be as large as in any form of leukemia; but, as a rule, it is not so, being only slightly larger than normal, and containing perhaps circumscribed lymphomas. The disease corresponds rather to chronic lymphemia than to the other types of leukemia, in respect of the changes in the organs; that is, we usually find circumscribed lymphomas as metastases, rather than diffuse infiltration such as would produce great enlargement of organs, like the spleen and liver. The distribution of metastases may be as wide as in lymphemia, and there is no organ or surface—serous, mucous, or epidermal—that may not be invaded. Gastro-intestinal forms of the disease have been described.

Microscopically we find in all advanced cases, first, a great increase of stroma in the lymphadenoid organs, then the hyperplasia of lymphoid cells, as described in leukemia. Goldmann noted the presence of a zone of eosinophiles outside of the boundary zone of small lymphocytes in the follicles. The writer has not seen any account of marrow elements in the lymphomas or metastases, most observers not taking the pains to decide this point.

THE CIRCULATORY SYSTEM.

THE ORGANS OF CIRCULATION.

THE HEART.

Congenital Abnormities.—Malpositions of the Heart.—The most serious form of malposition of the heart is *ectopia cordis*, a condition in which the organ is situated outside of the thorax. In *ectopia cordis pectoralis*, the sternum is divided longitudinally by a median fissure, in which case the heart is entirely exposed or covered merely by the integument; in grave cases life is of short duration. In *ectopia cordis abdominalis*, the organ is situated below the diaphragm; it may be found between the stomach and abdominal wall, in the neighborhood of one of the kidneys, or with other viscera in an umbilical hernia. Patients with this anomaly may live for years; Peacock reports a case in a man forty-seven years of age. In *ectopia cordis cervicalis*, the heart is in the neck, under the ramus of the jaw. In this condition, extra-uterine life is short.

There are other misplacements of the heart, of a less serious nature; thus, it may occupy a median position, as in the fetus, or it may lie transversely. Again, the organ may lie on the right side of the body (*dextrocardia*), in which case there is usually a similar transposition of the abdominal viscera (*situs viscerum inversus*).

Abnormities in Size.—As Rokitsansky, Virchow, and others have pointed out, hypoplasia of the heart and arteries is sometimes found in association with chlorosis; it is also a usual accompaniment of the lymphatic constitution—*i. e.*, a condition in which there is hyperplasia of the lymphoid tissues and persistence of the thymus gland. Congenital hypertrophy of the heart is usually a sequence of fetal endocarditis, or is an accompaniment of some malformation, such as septal defect or stenosis of one of the large vessels. Very rarely no other abnormality is present to account for the hypertrophy; and under these circumstances the condition is to be regarded, according to Virchow, as an example of a diffuse myomatous neoplasia.

Defects and Diverticula of the Pericardium.—Deficiency of the pericardium may be complete or partial; it is usually associated with other vices of development, particularly with *ectopia*. Congenital diverticula are rare; they consist in a protrusion of the serous layer through the fibrous portion, which is unnaturally thinned.

Defects of the Auricular Septum.—Complete absence of the auricular septum is a rare deformity, and makes the heart a trilocular organ; or, in case the ventricular septum is also wanting, a bilocular organ. More commonly the septum is only in part deficient, and in these cases the foramen ovale may be closed or patent.

Patent Foramen Ovale.—This is one of the most common defects. It may exist alone; in which case, no serious disturbances may follow.

Generally, however, there are other abnormalities, such as stenosis of the pulmonary artery or a defect in the ventricular septum. In some instances delicate cords, resembling the chordæ tendineæ, are stretched across the open foramen.

Defects of the Ventricular Septum.—This deficiency may be complete or partial, more commonly the latter. Very often there is a single round or oval opening in the pars membranacea or “undefended space.” In other instances the two ventricles communicate through several openings. Defects of the ventricular septum are usually associated with a patulous state of the foramen ovale and abnormalities of the large vascular trunks, such as stenosis of the aorta or pulmonary artery, or transposition of these vessels.

Stenosis and Atresia of the Pulmonary Artery.—Constriction of the pulmonary artery may be complete or partial; the former is rare, while the latter is common. The narrowing may involve the trunk of the vessel, the conus arteriosus, or the orifice. Stenosis, especially when it involves the orifice or the conus, is often the sequence of a prenatal inflammation. Atresia, on the other hand, is probably the result of an abnormal division of the truncus arteriosus. In many cases the ventricular septum is deflected considerably to the left, sometimes to such a degree that the aorta springs from the right ventricle. The latter is often much enlarged, not only at the expense of the left ventricle, which is unduly small, but also from an actual hypertrophy, the result of the extra demands made upon the right ventricle. When, however, the atresia develops after the closure of the ventricular septum (third month), it gives rise to hypertrophy of the left ventricle, as the latter in such a case must carry on both the systemic and the pulmonary circulations. Constriction of the pulmonary artery is usually associated with a patulous foramen ovale or an incomplete ventricular septum and a pervious ductus arteriosus, through which the blood is carried to the lungs.

Stenosis and Atresia of the Aorta.—All degrees of constriction of the aorta are observed, from slight narrowing to complete obliteration. The stenosis may involve the left conus, the orifice, or the arch near the ductus arteriosus. Waldstein has collected 113 cases of narrowing and closure of the aorta at or near the ductus arteriosus. In marked stenosis or atresia of the orifice, the ventricular septum being closed, the ductus arteriosus and the foramen ovale usually remain open, so that the right ventricle carries on both the systemic and pulmonary circulations through the pulmonary artery. In constriction of the arch between the ductus arteriosus and the left subclavian, the collateral circulation is effected by means of anastomosis between the branches of the subclavian and the descending aorta.

Transposition and Malposition of the Large Blood-vessels.—Occasionally the pulmonary artery is derived from the left ventricle, and the aorta from the right ventricle. More frequently, from a deviation of the septum to one side or the other, the two vessels have their origin in the same ventricle. These abnormalities are usually associated with a patent foramen ovale and a pervious ductus arteriosus. Sometimes the septa are also defective.

Persistent Ductus Arteriosus.—A pervious ductus arteriosus is a common accompaniment of septal defects and stenosis or atresia of the large vessels. When it exists as the sole lesion, it is not incompatible with long life. Sometimes the perviousness is only partial; in some instances the duct has been found aneurysmatically dilated.

Malformation and Defects of the Valves.—The most common valvular anomalies are those which affect the number and size of the segments. Union of the segments is occasionally encountered at the auriculoventricular valves, and may be the result of a malformation or a fetal endocarditis. There may be two or four semilunar valves, instead of three; the presence of two is usually due to an ancient endocarditis that has altered two of the leaflets in such a way that they form one large pocket.

THE PERICARDIUM.

Hydropericardium.—Hydropericardium, or dropsy of the pericardium, consists in an antemortem accumulation of serous fluid in the pericardial sac, independent of any inflammatory changes. As a rule, a small quantity of clear fluid is found postmortem in the pericardial sac, irrespective of the cause of death. This transudation is devoid of pathologic significance; it takes place naturally during the agonic period or shortly after death, and usually amounts to from 10 to 20 c.cm., or occasionally even to 100 c.cm. When the accumulation is in excess of these quantities, it has probably been formed antemortem; and under such circumstances, it is regarded as true dropsy.

The causes of hydropericardium are such as give rise to serous infiltration in other parts of the body; thus, Bright's disease and chronic heart disease are the most important factors. It is sometimes dependent upon a grave anemia or some general condition affecting the blood, such as tuberculosis, cancer, or scurvy. Aortic aneurysms, mediastinal tumors, chronic pulmonary affections, and chronic mediastinitis occasionally lead to stasis in the pericardial veins and to serous exudation into the pericardium.

The amount of fluid varies from a few ounces to a pint or more. It is usually clear and of a pale yellow or greenish hue. Slight turbidity may be occasioned by the presence in large numbers of desquamated endothelial cells. In rare instances the fluid is milky from admixture with chyle (chylopericardium). In cachectic states the effusion may be red from the presence of blood; and in jaundice it is dark yellow from the presence of bile. Degeneration of the surface endothelium and maceration of the pericardium may result from prolonged contact with the fluid.

Hemopericardium.—The accumulation of blood in the pericardium, independent of inflammation, may result from wounds of the heart; from spontaneous rupture of the heart; from rupture of aneurysms of the aorta, pulmonary artery, or coronary arteries; or more rarely from some general disturbance which affects seriously the blood-crisis, such as scurvy, purpura, or leukemia.

Under certain conditions the effusion in pericarditis may be mixed with more or less blood. This is commonly the case when the inflammation is dependent upon tubercle or cancer, or is associated with some grave cachexia.

The quantity of blood extravasated varies from a few ounces to several pints. Large accumulations are usually associated with small openings, since the movements of the heart are not arrested so quickly when the distention of the sac is gradual as when it is sudden.

The appearance of the blood is variable; it may be fluid or partly clotted. Not infrequently, when the condition does not prove immediately

fatal, inflammatory changes are excited in the pericardium by the presence of the blood.

Pneumopericardium.—Pneumopericardium, or the accumulation of gas in the pericardium, is an extremely rare affection. As in nearly every instance the air is associated with a certain amount of fluid, generally serum or pus, the condition is more correctly termed hydropneumopericardium or pyopneumopericardium. About one-half of the recorded cases have resulted from traumatism, the pericardium having been torn by a penetrating wound of the chest, a fractured rib, or a foreign body impacted in the esophagus.

The next most frequent cause has been the entrance of air through extension to the pericardium of some ulcerative process in a neighboring air-containing organ; thus it has been produced by a pneumopyothorax, or a phthisic cavity in the lung, an ulcer in the esophagus, or a gastric ulcer or cancer.

Cases are now and then encountered which have resulted from the decomposition of a purulent effusion by gas-producing bacteria.

Acute Pericarditis.—**Etiology.**—Excepting the rare cases in which inflammation follows some direct injury, pericarditis may be regarded as a secondary process. Rheumatism is by far the most frequent cause of the disease; of 100 cases analyzed by Sears, 51 were directly associated with acute rheumatism. While pericarditis may develop in the mildest type of rheumatism, there is greater liability to it when several joints are affected and the constitutional symptoms are severe. It is not an uncommon complication in various septic processes and specific fevers, such as septicemia, pyemia, gonorrhea, scarlet fever, chorea, and small-pox. Constitutional diseases, like gout, diabetes, and scurvy, are occasional antecedents. Involvement of the pericardium by extension of disease from adjacent structures is of frequent occurrence. Thus, pneumonia or pleurisy, especially when on the left side, may be followed by pericarditis. Pneumonia was the cause in 18 of Sears's cases. Osler found pericarditis in 5 of 100 fatal cases of pneumonia; in 4 of these the lappet of the lung overlying the heart was solidified. In some instances the inflammation results from the extension of acute myocarditis or endocarditis, but when these diseases are associated it by no means follows that the pericarditis is secondary; it may be primary, or, as is doubtless often the case, it may have developed independently from the action of the same morbid agents that caused the other cardiac lesions. Now and then pericarditis is secondary to such affections of neighboring parts as caries of the ribs or sternum, suppurating lymph-glands, mammary abscess, or ulceration of the esophagus. In these conditions, invasion of the pericardium may be effected through an actual rupture of the serous membrane, though this is exceptional. As the pericardium covers a large part of the ascending portion of the arch of the aorta, aneurysm in this locality may set up adhesive inflammation. Several cases are recorded in which an acute attack of pericarditis developed after occlusion of the coronary arteries by an embolus or thrombus. Finally, the primary focus of irritation may be located below the diaphragm; thus, an ulcer of the stomach may not only cause adhesion of the pericardial membranes, but may actually rupture into the pericardial sac. Of 20 cases of penetration of the diaphragm by gastric ulcer, collected by Pick, in 10 the ulceration had perforated the pericardium.

Bright's Disease.—Pericarditis may be encountered as a complication in

any form of nephritis, but is most frequent in the acute nephritis of adults and in chronic interstitial nephritis. The opinion has long been held that this form of pericarditis is the result of a toxic state of the blood arising from a failure of the eliminatory power of the kidneys, and this view has received support from the fact that the disease has developed in many instances when the phenomena of uremia were well pronounced; but until more thorough bacteriologic studies of the pericardial effusion have been made in these cases, a complete acceptance of the uremic origin of the inflammation is unwarranted. Indeed, it is well known that local infections are of common occurrence in the course of severe visceral diseases, and it seems not unreasonable to suppose that pericarditis developing under such circumstances is often of a microbic nature. This view has received some confirmation in a study recently made by Baillet, who, in a fatal case of uremic pericarditis, obtained a pure culture of streptococci from fluid drawn from the pericardial sac two hours after death and under strict precautions to prevent any accidental contamination. On the other hand, Banti did not find any bacteria in the pericardial exudate in nephritis and uremia.

Traumatism.—Contusions of the chest, fracture of the ribs, and penetrating wounds are occasional causes of the disease. In exceptional cases the pericardium has been wounded by foreign bodies impacted in the esophagus.

Bacteriology.—The micro-organisms most commonly associated with pericarditis are the different kinds of streptococci and staphylococci, the pneumococcus, and the tubercle bacillus (see Tuberculosis of the Pericardium).

Inflammation of the pericardium is invariably accompanied by more or less exudation, and, according to the character of the latter, three principal varieties may be recognized: serofibrinous, fibrinous, and purulent.

Serofibrinous Pericarditis.—In mild forms of pericarditis the serous membrane is more or less injected and lusterless, and covered in circumscribed patches or even throughout with a delicate gauze-like membrane, which can be readily peeled off with a knife-blade. Minute extravasations are often noted, which have resulted from the rupture of new blood-vessels. The serous exudation may be inconsiderable, in which case the term *dry pericarditis* is not inappropriate. Often, however, the serum is far in excess of the fibrinous exudation, the quantity varying from a few ounces to one or more pints. The fluid presents a great variety of appearances: Most commonly it is clear, transparent, and of a yellow or greenish color. In other cases it is more or less turbid or even opaque, from the abundance of corpuscles and fibrin. The latter may float free in the form of minute particles, slender threads, or curdy flakes. Sometimes, particularly in tuberculous or cancerous cases or where the inflammation accompanies some grave cachexia, the fluid is dark red from admixture with blood (*hemorrhagic pericarditis*).

The fluid has the usual characteristics of inflammatory serum; that is, it is of an alkaline reaction, contains from four to five per cent. of proteids, and has a specific gravity averaging about 1.020. This variety of pericarditis is most frequently excited by rheumatism, Bright's disease, tuberculosis, or chorea. It may end in complete recovery by the absorption of the effusion and the subsequent restoration of the serous surfaces to a normal condition. When, however, the fibrinous exudate is present in considerable quantity, perfect resolution is rarely effected. In such cases, after

absorption of the fluid, the opposing surfaces become more or less closely knit by firm adhesions. Circumscribed deposits of fibrinous material, instead of resulting in adhesions, may leave behind, on the surface of the heart, dense white opaque patches, which have been termed *milk-spots*.

Fibrinous Pericarditis.—This variety is characterized by the exudation of comparatively little fluid, but of large quantities of fibrin. The latter is generally more abundant on the epicardium, and may be limited in distribution to the auriculoventricular grooves or the posterior walls of the ventricles; but in many instances it is widespread and involves the whole surface of the heart. It is generally of a yellowish-white color: when newly formed, it is soft and can be readily detached; but when old, it is firm and tenacious. On account of the constant action of the heart, the surface is rarely smooth, but presents a velvety, tripe-like, or shaggy texture. This appearance has often been likened to that produced when two pieces of buttered bread are brought together and then forcibly separated.

In this form of pericarditis the exudation is rarely absorbed, but is organized into firm adhesions which may persist in the form of fibrous bands, uniting here and there the opposing surfaces of the pericardium, or which may be so universal as to cause a complete obliteration of the pericardial sac.

Microscopically the newly formed exudate consists of fibrillated or granular fibrin infiltrated with leukocytes. The endothelium beneath the exudate is more or less desquamated. The sub-endothelial connective tissue is crowded with leukocytes, and its blood-vessels are distended. Later the fibrinous deposit is invaded by spindle-shaped or stellate cells (fibroblasts) derived from the original connective tissue, and by new blood-vessels derived from the epicardial capillaries, and a granulation-tissue is thus formed which is ultimately converted into fibrous adhesions.

Purulent Pericarditis.—Purulent effusion in the pericardium usually follows general pyemic infection or a suppurating process in some neighboring structure; but pneumonia, tuberculosis, and the acute specific diseases not infrequently excite it. It is more common in children than in adults. The amount of pus varies from a few ounces to two or three pints. It may be thick and creamy, but it is often more limpid from admixture with a certain proportion of serum (*seropurulent pericarditis*).

A variable amount of soft fibrin is found floating in the pus and closely attached to the surface of the heart. In rare instances the pus undergoes decomposition and acquires a fetid, disgusting odor (*putrid pericarditis*).

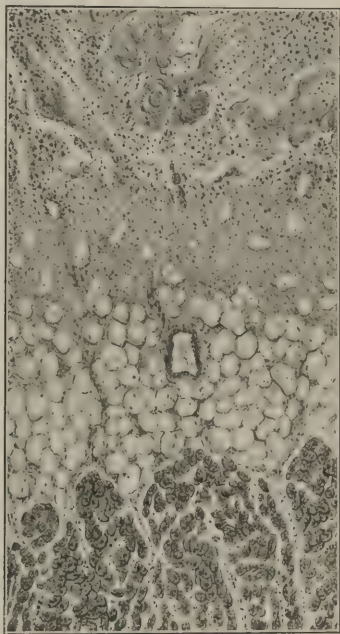


FIG. 162.—Acute fibrinous pericarditis.

Purulent pericarditis usually terminates fatally during the progress of the disease; it must be admitted, however, that recovery may take place in rare instances, even without evacuation of the pus. In these cases the fluid element of the exudation is absorbed, leaving a solid residue which is subsequently reduced to an amorphous mass. Finally a calcareous plate may be formed by the deposition of lime salts.

Cases are on record which have terminated in the perforation of the chest-wall or neighboring organs. Artificial evacuation of pus, when successful, results in fibrous union of the pericardial surfaces.

Fibrous Pericarditis.—This form is essentially chronic, and is most commonly observed in children and young adults. It generally results from the organization of the fibrinous deposits formed in acute and subacute attacks of pericarditis, but in some instances its onset is quite insidious. According to the extent and distribution of the fibrous overgrowth, four subdivisions of the forms of pericarditis may be recognized:

1. In this group are included those cases in which the adhesions are only partial and exist as fibrous bands of various lengths, uniting here and there the two surfaces of the pericardium. The length of these filaments being determined more or less by the radius of the heart action, the longer ones are usually found near the apex and the shorter over the auricles. Sometimes the contractions of the heart serve to detach one end of a filament, so that it lies free in the pericardial sac. The pericardium itself is usually somewhat thickened and indurated.

2. In some instances the adhesions are so extensive that the pericardial surfaces are universally adherent and united to the heart, the sac being completely obliterated. To this condition the term *adherent pericardium* has been applied. When recent, the adhesions are friable, and with care the surfaces can be separated; but when old, they become exceedingly tough, and separation cannot be effected without tearing away some of the cardiac muscle. The pericardium itself is often considerably thickened, so that the fibrous covering of the heart may measure from a quarter- to a half-inch in thickness. Very rarely calcification follows, converting the whole mass into a bony capsule.

3. There is a group of interesting cases in which the adhesions are not confined to the pericardial sac, but involve also the external surface of the pericardium, thus firmly uniting the heart to the chest-wall, pleura, diaphragm, or mediastinal structures. This condition has been termed *indurative mediastinopericarditis* or *external pericarditis*. It is more common in adults than in children, and of 36 cases analyzed by Whipple, 28, or more than two-thirds, were in males. The origin of the affection is often obscure. In only a few cases has there been a definite history of a previous attack of acute pericarditis.

Undoubtedly tuberculosis of the mediastinal lymph-glands, lung, or pleura has often played an important part in its development.

Some cases have followed traumatism or one of the acute fevers, most commonly scarlatina or measles.

The fibrous hyperplasia is not always confined to the chest, but often extends below the diaphragm and involves the peritoneum, especially those portions reflected over the liver and spleen.

In a few instances, as in a case cited by Roberts, the adhesions have been entirely external, the pericardial sac being free throughout. In 11 of 36

cases collected by Whipham there was enlargement of the heart; in nearly every instance there was enlargement of the liver from venous congestion; in 5 cases there was enlargement of the spleen; and in 11 of the 21 cases in which the subject was alluded to, serous effusion accompanied the proliferative peritonitis.

4. Occasionally cases are observed in which there are few if any adhesions, either internal or external, the pericardial layers alone being the seat of fibrous overgrowth.

Effects and Associated Conditions.—The disturbance produced by effusion in the pericardium cannot be said to be altogether proportionate to the quantity, since often at the autopsy several ounces of fluid are found in the sac, whereas nothing in the clinical history has suggested its presence. When, however, the amount of fluid is considerable, certain mechanic effects necessarily follow from pressure upon the chambers of the heart, the large vessels communicating with it, and even contiguous structures.

Changes in the myocardium are rarely absent, and it is to these, more often than to the lesions of the pericardium itself, that the serious sequels of pericarditis are to be attributed. As a rule, only that portion of the heart-muscle adjacent to the pericardium, inward to a depth of 1 or 2 mm., is affected; but at other times the lesions are more general and involve the entire myocardium. The fibers are the seat of fatty and parenchymatous degenerations, and the connective tissue between them is infiltrated with round cells. At a later period the appearances are those of fibrous myocarditis. While these changes are undoubtedly often secondary to the pericarditis, there are times when they are so disproportionate to the latter and so far removed from the surface as to warrant the belief that they have developed coincidently from the action of the same morbid agent which has invaded all the structures of the heart, including not infrequently the endocardium. Fibrous pericarditis, especially indurative mediastinopericarditis, is often associated with considerable hypertrophy or dilatation of the heart, but not so commonly as formerly supposed. Enlargement was present in but 11 of the 36 cases tabulated by Whipham. The cause of this enlargement has evoked considerable discussion; it seems likely, however, that the factor responsible for its production is not always the same. Broadbent believes that dilatation results from the myocarditis accompanying the original attack of pericarditis, and that subsequent organization of the adhesions effectually prevents the heart from again recovering its normal size. In some instances coexisting valvular disease or constriction of the large vessels by fibrous bands may be an important factor in bringing about enlargement. Finally, it is not improbable that the mere impediment offered to the movements of the heart by adhesions to contiguous structures may be productive of hypertrophy.

The right ventricle is usually more seriously affected than the left, and, according to Broadbent, for the following reasons: First, the right ventricle, on account of its weak contractile power, is less able to free itself from adhesions while in process of formation, and, when adhesions are formed, less able to contract against them and fully complete the systole; secondly, the thin-walled right ventricle has less chance of recovering from the effects of myocarditis than the left, where there is much greater thickness of muscular substance; and thirdly, as adhesions are more apt to unite the heart

in front to the chest-wall and below to the diaphragm than behind to the vertebral column, it follows that the right ventricle, from its anatomic relations, must suffer more than the left.

Occasionally, instead of enlargement of the heart, there is atrophy or hypoplasia. This condition has been noted most frequently where the pericarditis has occurred in early childhood, and has led to the formation of dense adhesions which have obliterated the sac of the pericardium, and so compressed the heart as to arrest its growth.

Pericarditis is often associated with endocarditis, particularly in children. It is possible for either affection to be primary, and the other secondary; generally, however, the two are to be considered as having resulted independently from the action of the same agent.

Tuberculosis.—Tuberculosis of the pericardium, when not a part of a general infection, is usually secondary to tuberculosis of the lungs or of the mediastinal lymph-glands. The condition may be acute or chronic, and the exudation may be serofibrinous, fibrinous, purulent, or hemorrhagic. There may be a marked production of new tissue and more or less distinct tubercles. There is often but little in the gross appearance of the lesions to indicate the tuberculous nature of the affection, and doubtless many of these cases have been regarded as nontuberculous and caused indirectly from exposure to cold and wet. But, as in the case of pleurisy, it seems highly probable that many cases of so-called primary pericarditis are the result of tuberculosis. It is true that tubercle bacilli are rarely discovered in the exudation; but it is now well recognized that pleurisy with an apparently sterile effusion is usually tuberculous. Eichhorst proved this to be true by inoculating guinea-pigs with large quantities (15 c.cm.) of the serous exudate. In this way 15 of 23 cases of acute pleurisy were shown to be tuberculous. In an earlier series of experiments the results were not so conclusive, as the quantity of exudate injected (1 c.cm.) was too small. In a similar manner the same investigator has shown that pericarditis is also frequently tuberculous, positive results having been obtained in 8 of 27 cases. He points out that, as the tubercle bacilli are often very scanty, ordinary culture and inoculation experiments are unreliable.

There is also a chronic obliterative pericarditis due to tuberculosis. It may, however, be impossible to determine the tubercular character without microscopic examination.

Actinomycosis.—Occasionally actinomycosis of the lungs, esophagus, mediastinum, or abdomen extends to the pericardium, whence it may invade the heart-muscle.

Tumors.—Tumors of the pericardium are rare. Carcinoma may invade the pericardium either by extension or metastasis. A few cases of primary sarcoma are recorded. J. C. Williams¹ has described a remarkable case of primary diffuse sarcoma of the parietal pericardium.

THE MYOCARDIUM.

Retrogressive Changes.—**Atrophy and Hypoplasia of the Heart.**—In atrophy of the heart, the organ is diminished in weight and size, from a loss of muscular substance. In hypoplasia, it has failed to reach its normal size, from defective development.

¹ *New York Med. Jour.*, April 14, 1900.

Atrophy may be total, involving the whole heart; or partial, involving certain chambers. Total atrophy occurs in the course of wasting diseases, such as cancer, phthisis, and diabetes. It is also an accompaniment of old age. Fibrous pericarditis occurring in young children may give rise to such dense adhesions that the heart is strangled and thereby effectually prevented from attaining its normal size. On account of a deficient blood-supply, partial atrophy affecting the left ventricle is sometimes observed in mitral stenosis. Finally, slowly developing stenosis of the coronary arteries is occasionally followed by partial atrophy.

As Virchow pointed out, hypoplasia of the heart and arteries is sometimes associated with chlorosis; but, apart from chlorosis, the heart is now and then found to be disproportionately small in subjects who during life gave no evidence of cardiac insufficiency.

In atrophy the heart is usually diminished in size as well as in weight. According to Wunderlich, an adult heart is to be considered atrophic that weighs less than 200 grams. Bramwell has recorded a case in which the heart weighed only $2\frac{1}{4}$ ounces (69 grams). The surface is often wrinkled, while the arteries are remarkably tortuous—appearances which are not observed in hypoplasia. The color of the muscle is variable; very often, however, it is quite brown from the deposition of pigment about the nuclei of the fibers (*brown atrophy*). A relative or actual increase of fibrous tissue may give to the walls of the heart an unnatural toughness. The pericardial sac often contains an excess of serous fluid.

Microscopic degenerative processes are always found to be associated with atrophy of the fibers. The latter in many places have lost their striations and are the seat of more or less extensive pigmentation and degeneration. Proliferation of the connective tissue is a marked feature in many instances.

Parenchymatous Degeneration.—Parenchymatous degeneration or cloudy swelling of the heart occurs in acute infectious diseases, like typhoid fever, diphtheria, septicemia, etc. It seems to be the result of a reaction between the cell protoplasm and the specific toxins of these affections. Whether high temperature itself can accomplish this transformation is an open question; it is probable, however, that the chief factors in effecting the change are poisons, even though they are in some instances the product of the febrile process rather than its cause. The changes peculiar to cloudy swelling are so intimately associated with other lesions of a degenerative or inflammatory character that it is often difficult to decide where the process begins and where it ends. As a simple transformation, it results in a swelling of the fibers, a disappearance of their striæ, and the deposition of fine granules, which, unlike fat, resist the solvent action of ether, but disappear on the addition of acetic acid. When these changes are not too profound, restoration of the cells to their normal condition is possible. When, however, the cause is severe and its action prolonged, disintegration becomes more pronounced, and other degenerative changes, such as fatty and hyaline, assist in the destruction of the cytoplasm. Finally, as an evidence of reaction, there is often present a round-cell infiltration of the intermuscular connective tissue.

When parenchymatous degeneration is well advanced and widespread, it may be revealed by certain macroscopic changes; the heart is pale and dull, its tissue is soft and flabby, and not infrequently its chambers are somewhat dilated.

Fatty Infiltration.—Fatty infiltration of the heart consists in an inordinate accumulation of fat upon the surface of the heart as well as between its muscular fibers. It is simply an excess of the fat which is normally

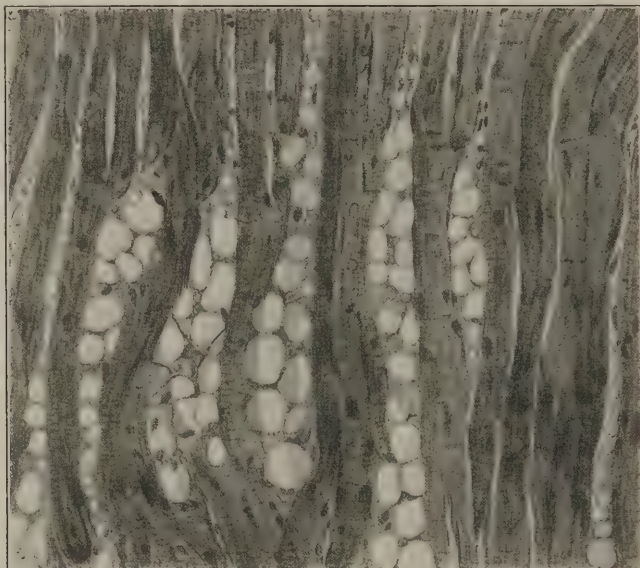


FIG. 163.—Fatty infiltration of the heart.

present in variable amounts beneath the epicardium, especially along the blood-vessels and in the grooves between the auricles and ventricles.



FIG. 164.—Fatty infiltration of the heart-muscle. The fat is stained orange with sudan III. The muscle-fibers are compressed.

As a morbid condition, it is most frequently observed as a part of general obesity in persons of advanced years. In some instances, it is due to the defective oxidation resulting from anemia or chronic pulmonary disease. When the infiltration is well marked, a large part of the heart, including

the entire right ventricle and a considerable portion of the left ventricle, may be encased in a thick capsule of fat. Over the base of the ventricles, where the most extensive deposits occur, there may be a distinct lobular arrangement. From the epicardium, fatty trabeculae may extend along the intermuscular fibrous septa as far as the endocardium, the amount gradually diminishing from the surface inward. Microscopic collections of fat-cells are everywhere interposed between the muscle-fibers. A high degree of fatty infiltration may exist for some time without affecting the integrity of the muscular substance of the heart; but ultimately, owing to compression of the muscle by the adipose tissue and to interference with its contractility, the fibers atrophy and become the seat of a true fatty metamorphosis. Rupture of the heart may take place from the replacement of the muscular walls by adipose tissue.

Fatty Degeneration.—The causes leading to the formation of fat in muscle-fibers of the heart are both local and general. The most important local cause is ischemia, from stenosis of the coronary arteries. The hypertrophied heart of chronic valvular disease is often the seat of more or less fatty changes of this kind; and, while the latter is usually regarded as the cause of the failing compensation, the possibility of its being, at least in part, the result of the cardiac insufficiency must be borne in mind. It is often observed in the outer layers of the myocardium in pericarditis.

The two general causes of true fatty metamorphosis of the heart-muscle are certain poisons and cachectic states. As examples of the former may be mentioned the toxins of various infectious diseases, such as diphtheria, scarlatina, and typhoid fever, and many mineral poisons, notably phosphorus, arsenic, and antimony. In the cachectic states are included all diseases which are associated with profound alterations in the blood, such as pernicious anemia, cancer, and phthisis. In some of these affections, however, the likelihood of a toxic action also must be considered.

Morbid Anatomy.—Fatty degeneration may be diffuse or circumscribed. Even when the cause is general, certain parts of the heart are usually more affected than others. As a rule, the ventricles, especially the left, are most seriously involved. The heart may be of any size, though naturally the tendency is toward dilatation. The macroscopic appearances are sometimes deceptive, and a heart that appears normal may show microscopically well-marked fatty changes. A change in color, however, from a dull yellowish-brown to a distinct yellow is generally observed. These colors may be uniform throughout or appear in streaks. The muscle is soft and flabby, and when cut imparts a greasy feel to the fingers. When the process is well advanced, the consistence of the organ is so much diminished that the tissue can be readily torn by the fingers. Indeed, in some instances, the immediate cause of death has been rupture of the heart under severe physical exertion.

Microscopically the muscle-fibers are found to be studded with fat droplets; these occupy the interfibrillary sarcoplasm and are disposed in rows

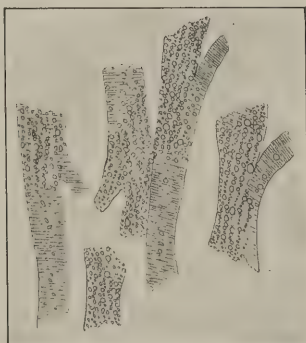


FIG. 165.—Muscle-fibers of the heart, showing fatty degeneration.

extending from the poles of the nucleus. The transverse striations are not necessarily affected; but when the condition has reached an advanced stage, the striæ as well as the nuclei may be obscured by fat. According to Goebel, these changes are usually most pronounced immediately beneath the epicardium and endocardium. In the acute infections, fatty changes in the muscle of the heart are always associated with other lesions, the most important of which are parenchymatous degeneration, vacuolization of the fibers, enlargement and segmentation of the nuclei, segmentation along the lines of the cement substance ("*myocardite segmentaire*"), and small-cell infiltration in the interstitial tissue.

In chronic cases, especially when the exciting cause has been sclerosis of the coronary arteries, the fibers are often atrophied and pigmented, and separated here and there by extensive deposits of fibrous tissue (chronic interstitial myocarditis).

Amyloid Degeneration.—Small areas of amyloid degeneration are not infrequently met with in the heart, but the process is rarely sufficiently extensive to be recognizable by the naked eye. As in other organs, the degeneration attacks the walls of the blood-vessels and the interstitial tissue. When the endocardium and pericardium also are involved, the size and weight of the heart may be considerably increased, and the amyloid deposits may be manifested macroscopically as nodules or seams composed of a dense, grayish, translucent material. An interesting case of this kind has been recorded by Ziegler. The patient was a woman of about fifty, who had died of heart failure. On postmortem examination it was found that the heart, all the mucous membrane, the peritoneum, tongue, and lungs were amyloid. The heart-muscle and the endocardium and pericardium were everywhere thickened and beset with numerous translucent, gristly nodules as large as millet seeds.

Other lesions are usually associated with amyloid degeneration, such as interstitial myocarditis, atrophy of the muscle-fibers, and fatty or hyaline metamorphosis.

Hyaline Degeneration.—Hyaline degeneration of the myocardium is characterized by the deposition of a clear, glass-like substance in the intermuscular connective tissue. It resembles amyloid degeneration, with which it is sometimes associated; but the hyaline material has not the same staining peculiarities as the amyloid. The affected areas may be either quite homogeneous or composed of close aggregations of minute semitransparent drops. Zenker, Rosenbach, Romberg, and others have described a transformation in the muscle-cells of the heart, after various acute infections, which they regard as a form of hyaline degeneration. The fibers are swollen and translucent, and the striæ are indistinct or lost. These changes are accompanied by fatty changes, cloudy swelling, and acute interstitial myocarditis.

Lesions of the Myocardium caused by Acute Infectious Diseases.—It is a well-established fact that acute infectious diseases, such as diphtheria, scarlatina, typhoid fever, and septicemia, may produce extensive alterations in the myocardium without necessarily involving the endocardium or pericardium. These alterations affect the muscular substance, interstitial tissue, blood-vessels, and nervous mechanism of the heart.

Allusion has already been made to the frequent occurrence of parenchymatous, fatty, and hyaline changes of the cytoplasm in acute specific diseases; other changes, however, involving the muscle-nuclei, have been

described by Oertel, Romberg, and others. These observers have found the nuclei enormously distended and elongated, or divided into numerous segments. The significance of these peculiar nuclei has not been determined, but Romberg and Ehrlich agree in regarding them as evidence of degeneration and not of multiplication. In addition to these changes, vacuolization and segmentation of the muscle-fibers are frequently seen.

The most important lesion of the interstitial tissue consists in its infiltration with round cells, either singly or in groups. These cells are found most abundantly about the blood-vessels, but their appearance inside of the muscle-bundles has been repeatedly observed. Romberg attaches considerable importance to this lesion. He believes that in cases of recovery from the acute diseases it may be followed by the formation of circumscribed fibrous patches, which may seriously impair the function of the heart and ultimately induce secondary change in the myocardium similar to those resulting from stenosis of the coronary arteries.

Important changes are sometimes observed in the blood-vessels of the myocardium; thus, there may be swelling of the intima, hyaline degeneration of the media, and leukocytic infiltration of the adventitia. The capillaries are overdistended, and small extravasations beneath the pericardium and into the parenchyma are not rare. The most significant vascular lesion, however, consists in the presence of hyaline thrombi in the small arteries. The effect of these occluding thrombi on the functional activity of the heart can be readily appreciated.

Only a few observations have been made concerning the changes wrought in the nervous mechanism of the heart by the specific fevers. In some cases the ganglia have been infiltrated with round cells; in other instances the ganglion-cells have shown a loss of their nuclei and fatty changes.

Segmentation and Fragmentation of the Myocardium.—Segmentation of the muscle-fibers, although alluded to by earlier writers, particularly by Zenker, was first carefully studied in 1877, by Renaut and Landouzy, who described it under the name of *état ségmentaire*. Lately it has received the attention of numerous investigators; in this country, of Hektoen¹ and J. B. MacCallum² especially. The frequency of its occurrence is attested by the fact that Tedeschi found it in 48 per cent. of 236 deaths from various causes, and Hektoen in about 65 per cent. of 190 consecutive cases in which an examination was made. A distinction is made between segmentation, which consists in separation along the natural line of union between the muscle-cells, and fragmentation, which consists in rupture of the fiber at any part of its course without reference to the cement lines. The two processes are usually associated, though not necessarily so.

Segmentation is very commonly found in the heart after sudden death from traumatism or suffocation, in connection with hypertrophy from its usual causes, and after many acute infections. The process may be local or general. The parts most frequently affected are the papillary muscles of the left ventricle and the septum. It is rare in the auricles. The appearance of the heart is variable and is dependent largely upon associated morbid conditions. When segmentation is the only lesion present, the organ may not appear abnormal. Very often changes characteristic of parenchymatous degeneration, of brown atrophy, or of chronic interstitial myocarditis are present. In simple dissociation the segments may consist of single cells or

¹ *Am. Jour. Med. Sci.*, Nov., 1897.

² *Jour. Exp. Med.*, iv., 409-424, 1899.

of isolated masses composed of a number of cells. While the ends are sometimes clean-cut, they often show uneven contractions or extensions.

The exact significance of segmentation is still undetermined; some pathologists regard it as a purely agonal or postmortem change, while others look upon it as an intravital process depending upon causes which have directly affected the integrity of the intercellular cement or which have influenced the latter by inducing nutritive changes in the muscle-cells. Hektoen closes an elaborate study of the subject with the following summary:

"The cardiac muscle-fibers frequently separate into muscle-cells and irregular fragments. Segmentation and fragmentation are due to disproportion between the vigor and order of muscular contraction and muscular cohesion. They occur in normal heart-muscle due to excessive vigorous and irregular contractions. More frequently they are encountered in association with acute and chronic secondary and primary myocardial changes that

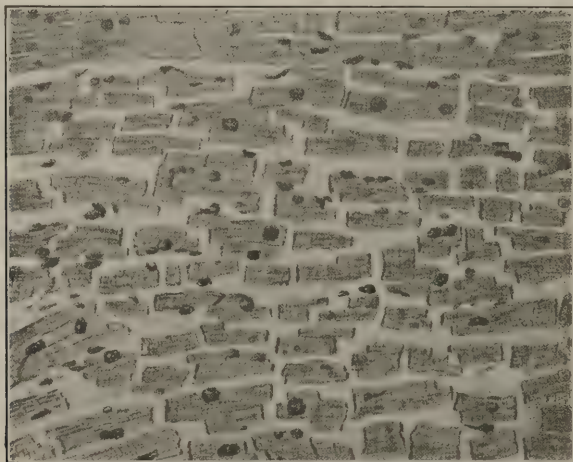


FIG. 166.—Segmentation of the heart-muscle.

alter the cement, weaken the plasma, and predispose to dissociation under normal or increased heart's action. General segmentation is of brief duration, because its occurrence is incompatible with further cardiac contractions. Local or limited segmentation may perhaps cause incompetency of the auriculoventricular valves, especially the mitral. It may lead to cardiac insufficiency and possibly to rupture of the heart. The fate of loosened muscle-cells is not known. It seems, however, that local dissociation is of but short antemortem duration. The occurrence of primary segmentation as a distinct disease is not known."

Progressive Changes.—Hypertrophy and Dilatation.—Hypertrophy and dilatation of the heart can be conveniently discussed together, since they are so frequently associated and since the causes of the one, with certain limitations, are the causes of the other.

Hypertrophy is enlargement of the heart, due to an increase of the muscular substance of the organ. It may be total, involving all parts of the

heart; or partial, involving certain chambers of the organ. Dilatation is increase in the size of the cavities of the heart, with or without thickening of their walls. Like hypertrophy, it may be total or partial.

Increased demands upon the function of the heart lead to hypertrophy or dilatation, the tendency to the one or the other being determined by the suddenness of the demand, its intensity, and the tone of the cardiac walls. Increased demands upon the entire heart, long-continued tachycardia, or frequent attacks of palpitation, such as occur in exophthalmic goiter or result from the excessive use of tobacco, may cause total hypertrophy. The latter is also observed in interstitial myocarditis and adherent pericardium. Prolonged physical exertion, while it often enlarges the whole heart, more particularly affects the left ventricle; and the same is true of chronic Bright's disease. The manner in which nephritis induces cardiac hypertrophy has long been under discussion, but our knowledge of the relation between the two affections has not advanced materially beyond the hypotheses formulated by Bright nearly fifty years ago. Bright says: "The obvious structural changes in the heart have consisted chiefly of hypertrophy, with or without valvular disease; and what is most striking, out of 52 cases of hypertrophy, no valvular disease whatsoever could be detected in 34; but in 11 of these 34, more or less disease existed in the coats of the aorta; still, however, leaving 22 without any probable organic cause for the marked hypertrophy generally affecting the left ventricle. This naturally leads us to look for some local cause for the unusual efforts to which the heart has been impelled; and the two most ready solutions appear to be either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately, or that it so affects the minute capillary circulation as to render greater action necessary to force the blood through the distant subdivisions of the vascular system."

The continued use of alcoholic beverages, a practice common among those who work in breweries, is productive of enlargement of the heart. Bollinger has recorded 42 cases of simple hypertrophy, without valvular diseases, which occurred among the workmen of Munich, and attributes the condition to the stimulating effect of the alcohol on the heart, to the overfilling of the vessels, and to increased nutrition.

Occasionally the ventricular walls are considerably thickened in still-born infants. Such a condition, existing without other circulatory abnormalities, is regarded by Virchow as a myomatous neoplasia of congenital origin.

Increased Demands upon the Left Ventricle.—Lesions affecting the aortic orifice are invariably followed by hypertrophy of the left ventricle. In stenosis the enlargement is due to the difficulty offered to the unloading of the ventricle; and in insufficiency, to the increased quantity of blood to be propelled from the chamber. Stenosis of the aorta (congenital or acquired) and general arteriosclerosis induce hypertrophy of the left ventricle. According to the investigations of Hasenfeld, arteriosclerosis only leads to hypertrophy of the left ventricle when the thoracic aorta or the splanchnic vessels are severely affected. Arteriosclerosis of the other vessels does not seem to have the same effect.

Increased Demands upon the Right Ventricle.—Lesions affecting the mitral orifice, and diseases of the lungs which interfere with the free entrance of blood from the heart, such as emphysema and fibrous pleurisy, are the

most common causes of hypertrophy of the right ventricle. Stenosis of the pulmonary orifice or of the pulmonary artery is a rare cause. In adherent pericardium the right ventricle is usually more affected than the left, for the reasons already given.

In the auricles hypertrophy is always associated with dilatation. Enlargement of the left auricle is usually dependent upon mitral disease, especially stenosis; and enlargement of the right auricle, upon some disease which obstructs the pulmonary circulation, or more rarely upon tricuspid stenosis.

Dilatation of the heart may precede hypertrophy or follow it. In the main dilatation is due to the same causes as hypertrophy; but it is more apt to develop than the latter when the strain is very severe and arises suddenly, or when the muscular wall of the heart is seriously affected. Interstitial myocarditis, even more than fatty changes, is the chief factor in lessening the resistance of the myocardium to the point where increased intracardiac pressure brings about dilatation of the cavities. That dilatation may follow hypertrophy without the appearance of microscopic lesions in the cardiac muscle is likely. Indeed, the microscopic changes in some instances may be the result of the failing compensation, instead of its cause. It seems likely that Cohnheim's view is correct, and that sometimes there is a simple fatigue or exhaustion of the fibers, unattended by any demonstrable histologic change. The inflammatory and nutritive changes in the myocardium incident to the infectious fevers not infrequently result in simple dilatation.

Morbid Anatomy.—Three varieties of cardiac enlargement may be recognized: (1) Simple hypertrophy, a form in which the muscle is thickened, but in which the cavity is of normal size; (2) excentric hypertrophy, or hypertrophy with dilatation, which is characterized by thickening of the muscle and an increase in the size of the cavity; (3) simple dilatation, in which there is thinning of the muscle and an increase in the size of the cavity. Some writers speak of a concentric hypertrophy, a form in which the muscle is thickened and the cavity is diminished in size; but such a condition seems to be more apparent than real, and is generally attributed to postmortem contraction.

The average normal weight of the heart in the adult is between 250 and 300 grams; in hypertrophy, however, the weight may increase threefold or even fourfold. A weight of 1980 grams in a case recorded by Stokes has probably not been surpassed. In simple and excentric hypertrophy, the thickness of the walls is often considerably increased. The wall of the left ventricle, instead of measuring from 7 to 10 mm., may measure from 20 to 25 mm.; and the wall of the right ventricle may be increased in thickness from a normal measurement of from 4 to 5 mm. to from 10 to 20 mm. The papillæ and trabeculæ usually share in the enlargement. The shape of the heart is also changed, according to the seat and degree of the enlargement. When the left ventricle is especially involved, the heart is elongated and extends more to the left. In enlargement of the right ventricle, the heart is increased in width and becomes more globular in form. The color and consistence of the muscle vary considerably, according to the state of nutrition. When quite healthy, the muscle is of a deep-red color and is resistant to the knife; when cut, the edges remain widely separated. Sometimes the color is more or less brown from pigmentary infiltration, or yellow from

fat. Fibrous changes make the muscular substance tough, while fatty changes make it friable.

Microscopically the individual muscle-cells are increased in size, and their number is probably also increased. Associated with the hypertrophy, there is often more or less connective-tissue hyperplasia or fatty degeneration.

Lesions of the Coronary Arteries.—Lesions of the coronary arteries play an important role in the production of myocardial disease. Being terminal arteries, occlusion of their branches by embolism, thrombosis, or arteriosclerosis throws the burden of sustaining nutrition in the affected part upon the neighboring capillaries and the vessels of Thebesius, which are usually so unequal to the emergency that degeneration or necrosis ensues.

Embolism and Thrombosis.—Complete occlusion, though it may be produced slowly by sclerotic changes, is usually the result of embolism or thrombosis. The location of the orifices of the coronary arteries near the root of the aorta, the angle at which these vessels diverge, and the force of the current at this point, are conditions which render the entrance of emboli of infrequent occurrence. Nevertheless, obstruction from this cause is occasionally encountered. The embolus usually consists of a piece of fibrin detached from one of the valves, especially the aortic, or from a cardiac thrombus; but occasionally it is made up of atheromatous pulp which has escaped from the vessel-wall some distance above the point of occlusion. The favorite location of emboli is in the anterior branch of the left coronary artery.

Thrombi are more common in the coronary arteries than emboli. Their formation is favored by sclerotic changes in the vessels; and, like emboli, they are most frequently found in the anterior branch of the left coronary artery.

Sudden occlusion of a large coronary branch may be followed by instant death; the cause of which, according to Porter, is the interruption of the entire cardiac circulation and the arrest of the heart in fibrillary contractions. When the obstruction does not prove immediately fatal, it may give rise to an area of anemic necrosis (*myomalacia cordis*), the favorite location of which is the wall of the left ventricle near the apex.¹ When recent such areas are irregular in outline, firm, slightly elevated, and of a yellowish color. Subsequently the patch softens and falls slightly below the surface of the heart. The endocardial surface of these infarcts is often covered with soft thrombi. Microscopic examination of the affected tissue reveals muscle-fibers in various stages of degeneration and disintegration, molecular debris, red and white blood-cells, and pigment granules. The appearance of granulation-tissue at the periphery is an evidence of regeneration. Such an area, if extensive, may end in rupture and the escape of blood into the pericardial sac; or, coincident with the absorption of the dead matter, new connective tissue may enter from the periphery and subsequently replace the anemic infarct with a fibroid cicatrix.

These circumscribed indurations are often of such a size that they can be readily recognized; on the other hand, small ones embedded in the heart-muscle are in danger of being overlooked unless the organ be thoroughly and systematically sliced. Finally, since the cicatricial tissue is less resistant

¹ For an experimental study of infarction of the heart, see Baumgarten, *Am. Jour. of Phys.*, ii., 243-264, 1899.

than normal muscle, a large scar may yield to the blood-pressure and form an aneurysmal dilatation.

Arteriosclerosis.—Sclerosis of the coronary arteries arises from the same causes which lead to sclerosis in other vessels. The obstruction occasioned by this condition develops slowly and leads usually to fatty degeneration of the heart, chronic interstitial myocarditis, or both. The stenosis may be more or less uniform throughout the vessels; or again, the constriction may be confined to the orifices, the main trunks, or the terminal branches. Chronic interstitial myocarditis, or fibroid induration of the heart, represents a replacement fibrosis: atrophy and destruction of the muscle being accompanied by a compensatory hyperplasia of the connective tissue. The process is usually most marked in the wall of the left ventricle near the apex, or in the septum. When diffuse, it is often associated with extensive hypertrophy.

Aneurysms of the Coronary Arteries.—Aneurysms of these vessels may result from sclerosis or embolism. They may be single or multiple, and vary in size from that of a millet seed to that of a cherry. Quincke reports a case in which he found twenty, varying in size from that of the head of a pin to that of a bean. The usual termination is rupture, generally into the pericardium, but occasionally into the ventricle, as in a case observed by Aran.¹

Aneurysm of the Heart.—The term aneurysm of the heart is applied to local dilatation of the cardiac walls or to pouch-like projections of the valves. While dilatation of an entire chamber of the heart is common, aneurysm is rare. Any lesion which diminishes the resistance of the muscle in localized areas may lead to this condition.

Aneurysm of the walls is usually due to the fibrous myocarditis resulting from coronary obstruction or to gummatous infiltration. Wounds of the heart, acute mural endocarditis, and fatty degeneration are rare causes. Rupture, however, is a more common termination of the last two conditions than local dilatation. According to Grandmaison, chronic adhesive pericarditis may be productive of aneurysm both by inducing fibrous myocarditis and by making traction on the walls. The anterior wall of the left ventricle near the apex is the usual seat. In 59 of 90 cases collected by Legg, it was in this situation. The septum is involved next in frequency; and when located here the aneurysm usually projects into the right ventricle on account of the greater force of the blood-current behind it. The walls of the right ventricle and of the auricles are very rarely affected; in only 3 of Legg's cases was the right ventricle the seat of the lesion. In size, aneurysms vary from that of a marble to that of the heart itself. Usually there is a single pouch communicating with the cavity of the heart by a large orifice, but in some instances the dilatation is saccular and the opening very small. A few cases have been recorded in which the aneurysm consisted of a series of intercommunicating sacs. The parietal layer of the pericardium is usually adherent to the sac, the walls of which represent the three layers of the heart, more or less replaced by fibrous tissue. The parietes of large sacs may be as thin as paper and completely devoid of muscle-fiber. Thrombi are usually found in the interior; they may be soft and granular or firm and laminated. The terminations are variable. In some instances, after reaching a certain size, they remain stationary. A few cases have been recorded

¹ See article by Capps, "Aneurysms of the Coronary Artery," *Am. Jour. Med. Sci.*, Sept., 1899.

in which the sac has been found completely filled with a firm clot. In a case of this kind reported by Wilkes the contents had undergone calcification. Very often, death results from cardiac insufficiency: to which, however, the aneurysm may be only contributory. It is remarkable how rarely rupture occurs, only seven of Legg's cases having ended in this way.

The dissecting aneurysm of the heart is an interesting form. It usually originates at the aortic orifice from ulcerative processes or traumatic rupture, and extends into the periaortic space of Vestberg.¹ Aneurysms in the beginning of the aorta may extend into the walls of the heart and become dissecting by secondary rupture. Vestberg distinguishes interparietal, septal, parietal, and valvular dissecting aneurysms of the heart.

Aneurysms of the valves may be acute or chronic, single or multiple. They are usually the result of ulcerative endocarditis; but sclerotic or atheromatous processes are sometimes responsible for their development. The bulgings are more or less spheric in shape, and project in the direction of the greater blood-pressure: those of the aortic segments protruding into the ventricle, and those of the mitral segments into the auricle. Although most authorities state that the aortic valve is much more frequently affected than the mitral, Drasche, who has carefully reviewed the literature of the subject, finds that they are more commonly located in the mitral valve, and that the anterior leaflet is more frequently affected than the posterior. Rupture of the valve, resulting in extensive insufficiency, is the usual termination in acute aneurysms. When large, they sometimes protrude into the blood-current and cause obstruction of the orifice presided over by the valve in which they are located. Small aneurysms sometimes give rise to no special disturbance, the endocarditis upon which they are dependent running its usual course.

Rupture of the Heart.—Spontaneous rupture of the heart is of rare occurrence. Krouskoff observed it but 3 times in 8000 autopsies. Mallett, writing in 1889, was able to collect only 179 authenticated cases. It is more common in men than in women. Of 115 cases tabulated by Odriozola, in 94 the age was over sixty, and in only 9 was it under fifty; but rupture of the heart has been met with as early as the tenth month. The accident has always occurred in a heart weakened by some pre-existing disease. Fatty degeneration with stenosis of the coronary arteries is the lesion usually encountered. Among the less frequent causes of rupture may be mentioned anemic necrosis from sudden occlusion of an important coronary branch, suppurative myocarditis, neoplasm, gumma, and echinococcus-cyst. In very rare instances the rupture has resulted from an affection acting upon the walls of the heart from without, as in the case recorded by McPhedran, in which an aortic aneurysm burst into the left auricle. In some cases the rupture has occurred during perfect repose, but more often mental excitement or physical exertion has been the determining factor. Thus, it has occurred during severe muscular effort, vomiting, coughing, defecation, or coitus. In one case it was excited by the passage of a stomach-tube, and in another by catheterization.

In 71 of 100 cases collected by Quain death was instantaneous. Sometimes, however, the rent is temporarily filled by blood-clot, and life is prolonged for several hours or even several days. Duplant records a case

¹ "Om dissekerande hjärtaneurismer," *Nordiskt medicinskt Arkiv*, Ny Följd, vii., Nos. 26 and 30, 1897.

in which the patient lived ten days after perforation took place. Such remarkable instances of prolongation of life after rupture of the heart, as well as the trivial character of the injury that sometimes leads to the accident, make this condition especially interesting from a medico-legal standpoint.

The rent occurs most frequently in the left ventricle, especially on the anterior aspect near the septum. According to Odrizola, the seat of the rupture in 132 cases was as follows: Left ventricle, in 96; right ventricle, in 22; right auricle, in 10; left auricle, in 2; and the auriculoventricular groove, in 2. As a rule, there is only one rent; in a few instances, however, two or more perforations have been discovered. The size and shape of the tear are variable, and depend to a great extent upon the condition of the myocardium and the seat of the lesion. The length of the opening ranges from a few millimeters to four or five centimeters. The fissure is more or less irregular in outline, often Y- or V-shaped; it usually runs in the direction of the muscle-fibers, and for this reason the internal and external openings are not often opposite each other. Not infrequently the tear is found in the wall of a cardiac aneurysm. In the neighborhood of the opening, fibrinous deposits are usually found; and these no doubt often serve to arrest the bleeding for a limited period. The amount of blood found in the pericardial sac varies from a few ounces to a quart or more. Death can rarely be attributed to the actual loss of blood; it is probably due either to disturbed innervation or to interference with the movements of the heart from the rapid accumulation of blood in the pericardial sac.

Inflammations.—Acute Myocarditis.—Acute inflammation of the myocardium usually follows one of the acute infectious diseases, such as diphtheria, scarlatina, rheumatism, and typhoid fever. It is very often



FIG. 167.—Acute myocarditis; segmentation; leukocytes between the segments. $\times 125$.

associated with acute endocarditis or pericarditis, and no doubt plays an important part in producing the serious symptoms which sometimes arise in the course of these diseases. In certain cases, however, the myocardium is the only part affected.

The inflammatory process is always accompanied with more or less parenchymatous or fatty changes of the muscle-fibers, but it appears to bear no definite relation to the latter. The essential lesion is the infiltration of the interstitial tissue with round cells. These cells are found especially about the blood-vessels, and appear singly or in groups. The veins and capillaries are dilated and contain an increased number of leukocytes. The left ventricle and the septum are usually the parts of the heart most seriously

affected. In two cases of acute rheumatic endocarditis, Romberg found cellular infiltration and thrombosis of many small arteries of the myocardium. As these changes were mainly in the vicinity of the auricular junction, the disturbing influence on the functional activity of the valves can be readily appreciated.

As to the terminations of acute myocarditis, it is likely that mild attacks end in complete resolution and the restoration of the heart-muscle to its normal condition; on the other hand, when the inflammatory process is severe, it is highly probable that the cellular infiltration becomes the foundation of a subsequent focal sclerotic myocarditis. Such a view is supported by the observations of Ziegler, Leyden, Romberg, and Lépine.

Acute Suppurative Myocarditis.—Acute suppurative myocarditis usually occurs in the course of some pyemic affection, especially ulcerative

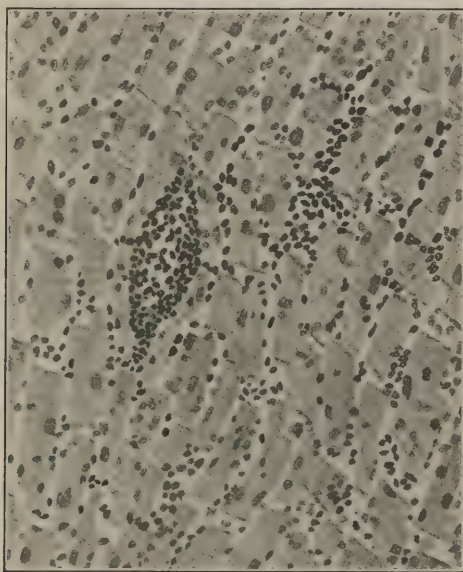


FIG. 168.—Acute suppurative myocarditis with miliary abscess; segmentation; cells between the segments.

endocarditis, the myocardium being involved through the entrance of infected emboli into the branches of the coronary arteries. In rare instances the disease results from the direct extension of a purulent pericarditis or malignant endocarditis. The process may be diffuse or circumscribed, the latter constituting abscess of the heart.

Macroscopically the condition is manifested by the presence of yellowish-gray spots or streaks, which may or may not be surrounded by a reddish zone of congestion. Sometimes these purulent collections are very numerous and widely distributed throughout the myocardium; but, as a rule, the left ventricle is more affected than the right. Abscesses varying in size from that of a pea to that of a marble are not uncommon. Roth reported one which contained 30 grams of pus. Microscopic examination of a small suppurating focus reveals a dense aggregation of leukocytes, disintegrated muscle-fibers,

and colonies of bacteria. In most cases abscesses of the heart are found intact, death having resulted from the disease which led to their development. In other instances rupture occurs into the pericardium or into one of the cavities of the heart. In this latter event septic emboli are carried into the circulation and give rise to metastatic abscesses in various organs, especially the spleen, kidneys, and brain. Occasionally the pus becomes inspissated and subsequently calcified. Acute cardiac aneurysm is another termination of circumscribed suppurative myocarditis. Finally, abscesses situated in the septa may establish communication between the cavities of the heart.

Chronic Interstitial Myocarditis (*Fibroid Induration of the Heart, Cardiosclerosis*).—The term chronic interstitial myocarditis is used to designate a condition in which the walls of the heart are the seat of a diffuse or circumscribed overgrowth of fibrous tissue. The affection is usually secondary to disease of the coronary arteries. Thus, in 18 of 21 cases cited by Steven, the arteries were found distinctly diseased. It occasionally happens that an area of anemic necrosis produced by the occlusion of an artery by an embolus or thrombus, instead of resulting in rupture of the heart, is gradually replaced by a new growth of fibrous tissue. More commonly, however, a slowly developing endarteritis is responsible for the sclerotic change. In some cases the obstruction is chiefly at the orifice of the vessel, the finer branches being only slightly altered; on the other hand, it is not uncommon to find a diffuse obliterating endarteritis with an orifice of nearly normal dimensions. It is questionable whether the term fibroid degeneration can be correctly applied to the fibrous hyperplasia accompanying this slow starvation of the cardiac muscle, since overgrowth of tissue can scarcely be considered a degenerative process. It is urged that it is equally inappropriate to use the term chronic myocarditis to designate an affection which is so conspicuously dependent upon a primary atrophy or degeneration of the parenchyma. It is conceivable, however, that the degenerate muscle itself may act as an irritant; and although the usual evidences of irritation may be wanting, this does not become a serious objection if we regard inflammation not as a series of unvarying phenomena, but as a process the essential factor in which is reaction to injury (Adami).

Fibrous myocarditis may be secondary to chronic endocarditis or pericarditis. In the first instance the papillary muscles are most frequently involved; in the second the superficial layers of the myocardium. In mitral disease, after a protracted period of imperfect compensation, the heart may show diffuse sclerosis with dilatation of the coronary veins and degeneration of the muscle-bundles. As a primary affection of the heart, chronic myocarditis may result from the reaction of poison of the muscle-substance to toxic agents brought to it directly through the blood. In this way the disease may be associated with chronic rheumatism, syphilis, or alcoholism. As was stated in discussing acute myocarditis, it is probable that the cellular infiltration which has been observed in the heart after typhoid fever, diphtheria, and other infections, is not rarely followed at a later period of life by focal sclerotic myocarditis.

In many instances the fibroid change is distinctly visible to the naked eye, and is manifested by grayish streaks between the muscle-fibers or as circumscribed white patches of a tough, leathery consistence. The favorite seats are the anterior wall of the left ventricle near the apex, the septum, and the tips of the papillary muscles. In some cases the fibrous change,

though quite extensive, is not so conspicuous, and indeed may be overlooked unless the wall of the heart is examined in serial sections.

Microscopic examination reveals an excess of connective tissue in the form of wavy bands running parallel with the muscle-fibers. The latter are usually more or less atrophied and often the seat of fatty or hyaline changes. When the process is well developed, it is usual to find areas of hyperplastic connective tissue devoid of muscle-cells. When associated with sclerosis of the arterioles, the tissue immediately around the affected vessels may be quite normal, while parts more remote show extensive transformation. The presence of small-cell infiltration is an indication that the process was still advancing when the patient died.

Chronic interstitial myocarditis may be associated with aneurysm of the heart, chronic endocarditis or pericarditis, hypertrophy and dilatation, or intracardiac thrombosis. Aneurysm of the heart is usually due to circumscribed cardiosclerosis, the weakened wall gradually yielding under the intracardiac

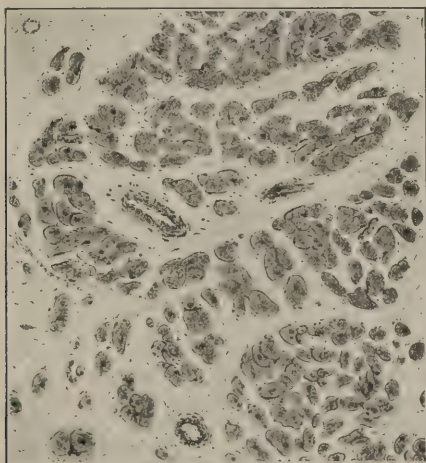


FIG. 169.—Chronic interstitial myocarditis.

pressure. It is probable that in every case of pericarditis the myocardium is involved to a greater or less depth, but in mild attacks the damage to the latter is inconsiderable; when, however, the pericarditis is of sufficient severity to cause extensive fibrous adhesions, the accompanying myocarditis is often intense enough to play an important part in developing the dilatation of the heart which is so apt to be a subsequent complication in these cases. Lesions of the valves are frequent in connection with fibroid changes in the myocardium. In some cases the two affections have developed simultaneously from the action of the same irritant. In a few instances it seems not improbable that a primary lesion of the papillary muscles has been responsible for the valvular insufficiency. Finally it has been shown that endocardial lesions themselves, by producing venous stasis, may give rise to a sclerosis having its starting-point in the vicinity of the dilated coronary veins.

Enlargement of the heart is a common accompaniment of cardiosclerosis; in one of Fagge's cases the organ weighed 35 ounces. The fibrous

overgrowth interferes with the ventricular contractions, and at the same time diminishes the resistance offered to the blood-pressure; so that the enlargement is due partly to hypertrophy and partly to dilatation.

Advanced disease of the myocardium is prone to excite the formation of intracardiac thrombi. The latter are most frequently found in the auricular appendices and in the muscular interlacement near the apex. A slight amount of fibrous change in the heart may give rise to no serious disturbance; but, when well marked, the usual termination is gradual failure of the circulation from cardiac insufficiency or sudden death in a paroxysm of angina pectoris.

Tuberculosis of the Myocardium.—Townsend, in 1832, was the first to record an example of tuberculous infection of the myocardium. In 1898 Hand collected 42 cases.¹ In nearly every instance a primary focus of tuberculous disease is found elsewhere in the body, especially in the mediastinal lymph-glands. Most of the cases have occurred before the fifteenth year. Infection may take place through the veins or by the spreading of a tuberculous pericarditis, but undoubtedly the most common avenue of invasion is through the lymphatics.

Anatomically the disease may be manifested in one of three ways: First and most frequently, as a circumscribed cheesy nodule, varying in size from that of a pea to that of a hen's egg; second, as semitransparent miliary tubercles disseminated through the cardiac muscle; and third, as a true tuberculous myocarditis, consisting of a diffuse sclerosis with giant cells and small round cells distributed between the muscle-fibers and the bands of connective tissue. The ventricles are more frequently affected than the auricles. The disease may be confined to the myocardium; but not infrequently the pericardium, and more rarely the endocardium, share in the tuberculous process.

Syphilis of the Myocardium.—Syphilis of the myocardium manifests itself as a more or less diffuse fibroid induration, as gummatous growths, or very rarely as amyloid degeneration. Fibroid induration or interstitial myocarditis is usually secondary to syphilitic endarteritis; but it probably can result from the direct action of the specific poison on the muscle-cells or their sheaths, since a few cases have been noted in which no lesion of the coronary arteries could be detected.

Gummatous growths are not so commonly found after death as syphilitic fibrosis; but it should be borne in mind that the latter condition, as well as aneurysm of the heart, quite frequently results from antecedent gumma. In the early stages gummas appear as yellowish or grayish cheesy nodules, varying in size from that of a pea to that of a marble, surrounded by a zone or capsule of dense fibrous tissue. Subsequently hardening or softening may occur, according as fibrous transformation or degeneration predominates. The wall of the left ventricle and the septum are most frequently attacked. The weakening of the muscular structure effected by the evolution of a gummatous growth is one of the causes of aneurysm of the cardiac walls. In many instances hypertrophy and dilatation of the heart, chronic adhesive pericarditis, and sclerotic endocarditis are concomitant conditions, and are usually secondary to the more important lesions of the myocardium.

Syphilis of the heart frequently ends in sudden death; 21 of 63 cases reported by Mráčák so terminated. The cause of the fatal syncope may be

¹ See also Moser, *Med. and Surg. Rep. of the Boston City Hospital*, xi., 194-203, 1900.

due to rupture of the heart or to occlusion of the coronary arteries by fibroid thickening or by an embolus derived from a softening gumma or from the contents of a cardiac aneurysm.

Foci of interstitial myocarditis occur in congenital syphilis.

Actinomycosis of the myocardium has been observed by Ponfick and others as the result of extension from the neighborhood or of metastasis.

Tumors of the Heart.—Tumors of the heart-muscle are rare; carcinomatous, sarcomatous, myxomatous, lipomatous, fibromatous, and myomatous growths are occasionally encountered. They may have their origin in the myocardium, or they may invade the latter from the pericardium or endocardium.

Carcinoma is always secondary; and sarcoma, with very rare exceptions, is also secondary. They may be single or multiple, and may appear as projecting nodules or as diffuse granular plates. Sarcoma is not infrequently secondary to a primary growth in the mediastinum, the pericardium being first invaded and then the cardiac walls. Osler describes a remarkable case of sudden death in a child in whom he found the tricuspid orifice firmly blocked by a sarcomatous mass that had come from the renal vein, the latter being filled with a sarcoma extending from a large tumor of the kidney.

Rhabdomyoma is congenital and occurs often as multiple tumors. The structure resembles that of embryonal heart-muscle.

True myxomatous tumors are occasionally observed, but most of the cystic formations found within the heart are softened thrombi. Polypoid growths are sometimes found protruding from the walls of the heart; most of these are organized thrombi, but others are of different origin, usually springing from the left auricular septum, and often, as in 6 of 11 cases collected by Pawlowsky, projecting through the mitral orifice into the ventricle. They are of a reddish color, and are covered by a smooth, shiny membrane. In addition to blood-constituents and fibrin, they often contain connective tissue and blood-vessels. The origin of these cardiac polyps is obscure; some have apparently consisted of varicose veins filled with organized clot, while others seem to have been the result of a hemorrhagic extravasation beneath the endocardium.

Small tumors of the heart may occasion no disturbance; but large growths may excite dilatation, valvular insufficiency, rupture, or embolism.

Animal Parasites.—In man the heart-muscle is rarely invaded by animal parasites; but the *Cysticercus cellulosæ*, *Pentastomum denticulatum*, and *Echinococcus* are occasionally seen. The last only is productive of mischief. In 155 cases of infection by the *Cysticercus cellulosæ*, Stiles found the parasite in the heart in 9 instances. In the 100 cases of echinococcus diseases occurring in the United States, compiled by Sommer, the heart was involved but once; but among 160 cases in which Davaine found echinococci in organs other than the liver, in 10 they were found in the heart.

Hydatid cysts vary in size from that of a pin-head to that of an orange, and may be single or multiple. They are more frequently found in the right ventricle than in the left. They sometimes rupture into the pericardium, or more commonly into one of the chambers of the heart, the contents being discharged through the aorta or the pulmonary artery. Oesterlen found the sac ruptured in 6 of 21 cases. In one instance gangrene of the right leg followed plugging of the femoral artery by hydatid vesicles discharged into the circulation from the rupture of a cyst in the left auricle.

THE ENDOCARDIUM.

Intracardiac Thrombi.—It is exceptional not to find at the necropsy a certain amount of coagulated blood in at least one of the chambers of the heart. This clot is most frequently found in the right auricle or ventricle, and is probably formed after death; although it is generally assumed, but without any evidence, that coagulation may occur also during the agonal period. Postmortem clots have certain characteristics by which they may be distinguished from thrombi; they are yellow or red, often particolored, the upper part being pale yellow and the dependent part dark red. They are soft, moist, translucent, and elastic; and being nonadherent, though often wrapped around muscular columns and cords, they are easily removed without damage to the endocardium. On the other hand, genuine thrombi are reddish gray, dry, brittle, opaque, and more or less adherent to the endocardium.

The causes of cardiac thrombosis are practically those of thrombosis of the blood-vessels, the important factors being lesions of the cardiac walls, slowing of the blood-current, and changes in the chemical composition of the blood; thus they are frequently found in hearts the seat of inflammatory, degenerative, and necrotic changes. Acute infectious processes, chronic diseases of the lungs and kidneys, and cachectic states also favor their development. Thrombi are more commonly found in the right chambers of the heart than in the left. In the auricle the favorite seat is the appendix; in the ventricle the neighborhood of the apex. Great variation is observed in the size and shape of thrombi. Some are so small as to be hidden between the muscular columns, while others are large enough to fill an entire chamber. Over focal lesions of the myocardium they may appear as flat, circumscribed deposits, often laminated, and firmly adherent to the heart-wall. In rare instances the mass is more diffuse and is spread over the inner surface of the heart like a false membrane. Among the most familiar examples of cardiac thrombi are the bead-like excrescences or vegetations which spring from the valves in acute endocarditis. Pedunculated thrombi (*Végétations globuleuses* of Laennec) are of common occurrence in the right ventricle. These have often been confounded with genuine polyps. They may be single or multiple. Their surface may be smooth or ribbed, and on section they frequently contain a thick, reddish-brown fluid. Very curious and rare formations are the so-called ball-thrombi. These are spheric masses, loose and freely movable, and varying in size from that of a pea to that of a large walnut. They may be solid throughout or cystic. In nearly all the recorded cases there was mitral stenosis and the thrombus was found in a dilated left auricle.

Secondary changes in thrombi are not infrequent; the most common is liquefaction, the interior of the thrombus being converted into a dark, grumous fluid. Calcification, with the formation of a *cardiolith*, is also possible.

Thrombi may remain indefinitely in the heart without seriously disturbing the circulation, but grave consequences may arise from the obstruction of one of the cardiac orifices or from embolism in an important organ.

Endocarditis.—**Acute Endocarditis.**—It is customary to divide acute endocarditis into simple or benign, and ulcerative or malignant; but no hard and fast line can be drawn between these forms. It was formerly supposed

that only the lesions of ulcerative endocarditis were associated with micro-organisms, and that their presence constituted a point of distinction between this and other varieties; but subsequent research showed conclusively that the vegetations of the so-called simple endocarditis were rarely free from the same micro-organisms. It is therefore generally conceded that the division of acute endocarditis into benign and malignant is not justified by pathologic differences; nevertheless, it is convenient, especially from a clinical standpoint, to retain these terms—bearing in mind, however, that they represent only the extremes in a process which manifests all degrees of intensity.

The most common preceding or associated disease in acute endocarditis is acute articular rheumatism. The exact proportion of cases in which these diseases are associated is difficult to determine, as the statistics must rest largely on clinical authority, which is by no means infallible. Bouillaud placed the percentage at 80, and Bamberger at 20. These figures may be regarded as the extremes, and it seems probable that a percentage between 40 and 50 would be not far from correct. While rheumatism so mild as to be readily overlooked may be complicated with endocarditis, yet the latter is more apt to develop when the rheumatism is severe and several joints are involved. Primary attacks of rheumatism are more frequently followed by endocarditis than subsequent attacks. Children with rheumatism are more prone to develop lesions of the heart than are adults. The mitral valve is most frequently affected, and only rarely does the process assume a malignant character. Endocarditis is occasionally met with in the course of tonsillitis, erythema nodosum, peliosis rheumatica, and certain other affections which seem to be related in some way to rheumatism.

Chorea plays a role in the etiology of the disease almost equal in importance to that of rheumatism. Osler found marked vegetations on the valves in 62 of 73 fatal cases of chorea. Endocarditis resulting from this cause is almost always of a benign type.

Septic and pyemic conditions, and the zymotic fevers, especially scarlet fever and croupous pneumonia, are not rarely complicated with acute valvular disease, which may assume either a benign or malignant character.

That endocarditis might occur in the course of gonorrhea was recognized long ago, but only within recent years has it been possible to determine the exact relation of the two affections. Bacteriologic investigations have shown that in some instances the disease was the result of a secondary infection by staphylococci or streptococci which had entered the circulation through the urethral lesion; in other cases, however, the endocardium seems to have been infected directly by the gonococci themselves. The latter cases were all of a malignant type, and, in 11 of 15 tabulated by Stengel, lesions were found in the aortic valves.

Rokitansky's teaching that there exists between the lesions of the heart and pulmonary tuberculosis a distinct antagonism can no longer be supported. Recent studies have established the fact that cardiovascular disease not only fails to give protection against tuberculosis, but, by producing favorable conditions, actually predisposes to it. Of 500 cases of tuberculosis compiled by Kidd, disease of the heart was found in 27. Of Frommhold's 277 cases of valvular disease, 22 (or 8 per cent.) had phthisis. Potain found pulmonary tuberculosis in 9 of 54 cases of mitral stenosis. Chevers and others have shown that tuberculosis is the most common cause of death in subjects with stenosis of the pulmonary orifice.

When the two diseases are found to be coexistent, it does not follow that the endocarditis is necessarily primary and the phthisis secondary. It has recently been shown that the former may supervene upon the latter. In these cases a careful bacteriologic examination is obviously of great value in determining which affection is primary.

While in most of the cases the inflammation of the valves seems to have been due entirely to a secondary infection, such as may occur toward the close of other wasting diseases, yet instances have been observed in which the bacilli of tuberculosis have been the only micro-organisms detected in the vegetations. The view that these bacilli may hold a causal relationship to the cardiac lesions is supported by investigations recently conducted by Michaelis and Blum. These observers set up aortic incompetence in rabbits by piercing the valves with an instrument introduced through the carotid artery, and subsequently injected tubercle bacilli into the vein of the ear. The animals died of general tuberculosis in from three to six weeks. A postmortem examination showed that the damaged valves were covered with soft vegetations in which tubercle bacilli were found in large numbers.

Traumatism.—Instances in which violent exertion or injuries to the chest have been followed by inflammatory lesions of the heart are sufficient in number to warrant the belief that traumatism itself can be an exciting cause. This belief is further supported by the experiments of Roy and Adami, who demonstrated that the increase of blood-pressure occasioned by applying a ligature lightly to the aorta was soon followed by inflammatory thickening of the valves; and also by the researches of Rosenbach, who showed that endocarditis could be excited by bruising the valves with a wire introduced through the carotid artery. Although it seems well established that a form of inflammation can result from injury, there is no substantial evidence to support the view that a true vegetative endocarditis can be occasioned by this factor alone; that is, without the aid of micro-organisms. On the contrary, the experiments of Wyssokowitsch and others clearly indicate that, when special care is exercised to prevent the entrance of bacteria, mechanic injury to the valves is powerless to produce characteristic vegetations.

Cachectic States.—A benign form of endocarditis sometimes develops toward the close of wasting diseases, such as cancer, phthisis, diabetes, and chronic nephritis. The inflammation in these cases doubtless belongs to that class of terminal infections to which sufferers from chronic diseases so frequently succumb. It is likely that the changes in the blood resulting from disturbed metabolism affect nutrition, and thus render the tissues more vulnerable; moreover, the studies of Flexner indicate that chronic diseases predispose to infection by impairing the bactericidal power normally possessed by the body fluids and cells in a state of health.

Malignant endocarditis is more apt to attack valves which are already the seat of sclerotic changes than valves that are perfectly healthy. The causes of this type of inflammation are the same, in the main, as those of the benign form. It is most frequently met with, however, in association with croupous pneumonia, septic infection, meningitis, or gonorrhea. Rheumatism, chorea, typhoid fever, tuberculosis, influenza, and diphtheria are rare causes. Biggs, Dreschfeld, and others have reported cases in which it developed after traumatism without external wounds. Its connection with gallstones, apart from suppuration, has been noted by Murchison, Netter and

Martha, Jaccoud, Leva, and others. In a few instances it seems to have developed as a primary infection, as no association with an antecedent disease could be traced.

Bacteriology.—Winge¹ in 1869 first demonstrated the presence of bacteria in the vegetations of endocarditis, and Heiberg² in 1872 corroborated this finding; Rosenbach in 1878 first induced the disease experimentally in animals, by injuring the valves by means of a sound passed into the carotid artery. This last observer also found in the valvular lesions the micro-organisms that had entered the circulation during the operation, and concluded that their presence was in part responsible for the growth of the vegetations, as the latter could not be attributed solely to the effects of the mechanic injury. Later investigators (Ribbert, Rodet, Dreschfeld, Roux, Josserraut, Michaelis, and others) showed that the disease could be induced simply by the introduction of various species of bacteria into the circulation without the aid of any previous injury or disease of the valves. Although both experimental and pathologic studies indicate that micro-organisms are the chief factor in the development of acute endocarditis, it is evident that no one species is to be held accountable for its production.

Of 29 cases studied by Weichselbaum, 7 showed the *Micrococcus lanceolatus*, 6 the streptococcus, 2 the *Staphylococcus pyogenes aureus*, 6 unusual bacteria, and in 8 the bacteriologic examination gave negative results. Of 19 cases studied by Stokes and Wright,³ 9 were associated with *Micrococcus lanceolatus*, 2 with streptococcus, 2 with *Staphylococcus pyogenes aureus*, and in 6 the results were inconclusive. In Flexner's 34 cases⁴ the *Micrococcus lanceolatus* and the streptococcus were found each 12 times, and the staphylococcus 3 times. It is therefore apparent that the chief offenders are the *Micrococcus lanceolatus*, the streptococcus, and the *Staphylococcus pyogenes aureus*. It is probable, however, that the above figures do not represent the exact etiologic relation of the various species of bacteria to acute endocarditis in all of its degrees of intensity, since in the main they are based upon the study of the infection as it develops in the course of grave or fatal diseases. Among other micro-organisms which have been found in the diseased valves may be mentioned the gonococcus, bacillus of tuberculosis, bacillus of diphtheria, *Bacillus coli communis*, *Bacillus pyocyaneus*, and bacillus of influenza.

In some instances the disease is apparently the result of a mixed infection, since two or more species of bacteria are found in the same lesions.

While it has been shown that the introduction of bacterial toxins into the circulation is capable of exciting various degenerative changes in the heart and blood-vessels, investigators have thus far failed to induce a true vegetative endocarditis without the presence of the bacteria themselves.

Morbid Anatomy.—Acute endocarditis much more frequently attacks the valves of the heart than the lining of the cavities. The mitral valves are involved first in frequency, then the aortic, tricuspid, and pulmonary valves. Lesions of the right side of the heart, acquired in extra-uterine life, are not so rare as formerly supposed. Sansom states, and Bramwell agrees with him, that the right side of the heart is affected in at least 50 per cent. of all acute inflammations of the endocardium and in almost every case of severe

¹ *Nordiskt medicinskt Arkiv*, 1870.

² *Virchow's Archiv*, lvi., 1872.

³ *Boston Med. and Surg. Jour.*, Mar. 21, 1895.

⁴ *Jour. of Exp. Med.*, 1., p. 559, 1896.

endopericarditis. These authors express the belief that the relative infrequency of chronic lesions of the tricuspid and pulmonary valves is due to the fact that resolution is more often effected on the right side of the heart, since its valves are subjected to less strain.

In severe forms of endocarditis it is not uncommon to find other parts of the endocardium involved, especially the chordæ tendineæ, the left ventricular aspect of the septum, and the posterior wall of the left auricle. The valves are generally first affected on the aspect facing the direct blood-current; that is, on the auricular surface in the case of the mitral valves, and on the ventricular surface in the case of the aortic valves. In neither are the lesions at the very edge, but along the line of maximum contact where there is greatest friction, and which is about 2 mm. from the free margin. The affected regions, which are at first only slightly rough and opaque, soon become studded with chains of delicate excrescences or vegetations. The latter are usually 2 or 3 mm. in diameter, and are lightly attached to the valves by slender pedicles. When recent, they are friable, grayish-pink in color, and almost transparent; when old, they are firm, white, and opaque. The microscopic appearances also vary with age. A section of the affected valve in the early stage of the process shows a superficial area of necrosis, void of nuclei, and overlaid with a fibrinous deposit, granular or fibrillar, enclosing a greater or less number of white and red blood-cells. When the section is properly stained, colonies of bacteria are frequently detected within the thrombus or in the upper layers of the endocardium. In the later stages, round-cell infiltration and proliferation of the connective-tissue elements are visible in the adjacent tissue. With the growth of the granulations beyond the surface of the valve, the original thrombus disintegrates and ultimately disappears. Not rarely, however, a secondary coagulum is subsequently formed over the inflammatory proliferations.

The term *warty* or *verrucose endocarditis* is used to designate a less severe form of infection, in which the necrotic process is limited and proliferation is more extensive than is required for the purpose of repair. When, however, necrosis is the prominent factor, and the reparative process is subordinate, the endocarditis is termed *ulcerative* or *malignant*. In such cases there is a marked loss of substance from the separation of the dead tissue and superimposed thrombi.

In the present state of our knowledge, it is impossible to state with absolute certainty the exact sequence of events that takes place in infective endocarditis; but it is probable that the first changes are of degenerative or necrotic character, that these are followed by the deposition of fibrin from the blood, and that subsequently, as a final reaction, a true inflammatory process is established, manifested by cellular exudation and proliferation.

Terminations.—In rare instances the vegetations undergo molecular disintegration or are slowly absorbed, leaving the valves so slightly damaged that their functions remain unimpaired. Usually, however, the thrombotic deposit is gradually replaced by fibrous tissue, which not only thickens the valves, but, by contracting, so shortens and distorts them that they are rendered, in one instance, obstructive to the onward flow of blood, and, in another, incompetent to close the orifice over which they preside. Finally the process is completed by the valve becoming the seat of calcareous infiltration and by the new fibrous tissue undergoing fatty or hyaline degeneration. Sometimes remnants of thrombi remain permanently attached,

undergo calcification, and thus still further interfere with the functions of the valves.

The detachment of a thrombus or the separation of a fragment of necrotic tissue is a common cause of embolism, the obstruction most frequently occurring in the brain, spleen, kidney, or arteries of the extremities.

Ulcerative endocarditis sometimes leads to valvular aneurysm or even to rupture of the valves or chordæ tendineæ; or, if it involves the mural endocardium, it may give rise to suppurative myocarditis or pericarditis, or it may excite aneurysm or rupture of the cardiac walls.

Associated Lesions.—The heart-muscle is probably more or less involved in every case of acute endocarditis. Romberg has emphasized the fact that the symptoms of acute endocarditis are not so much due to the valvular



FIG. 170.—Acute ulcerative endocarditis.

defects as to the associated lesions in the myocardium. In two cases of acute valvular disease of rheumatic origin, he found, in addition to some parenchymatous degeneration, acute interstitial myocarditis and hyaline thrombosis of many small blood-vessels. These lesions, particularly the occlusion of the small arteries, must contribute considerably to the disturbance of the heart's action in acute inflammation of the valves.

Pericarditis is likewise a frequent attendant upon acute endocarditis, particularly when the latter occurs in childhood. It was present in 34 of 161 cases of acute valvular disease observed by Sibson. Sturges states that of 100 fatal cases of heart disease occurring at the Children's Hospital within a period of ten years, of which 54 were of rheumatic origin, and 46 due to other causes, in 6 only was there no evidence of pericarditis.

Chronic Endocarditis.—Chronic endocarditis is often the sequence of a

previous acute attack. Not infrequently, however, the disease develops insidiously as the result of the long-continued action of some irritant which is apparently contained in the blood; thus it may be intimately associated with gout, chronic alcoholism, chronic lead poisoning, syphilis, or diabetes. Prolonged immoderate exertion is an important factor. In old age the disease often develops coincidently with sclerosis of the vessels, the two affections having a common etiology.

Morbid Anatomy.—The affected parts are slightly thickened, dull, and opaque. Sometimes along the edge of the valves there are slight nodular elevations, presenting a grayish-red appearance. Much more important is the puckering brought about by the contraction of the newly formed tissue; it is this which so seriously impairs the function of the valves.

Shortening of the chordæ tendineæ, which often share in the inflammatory process, also serves to restrict the movements of the auriculoventricular valves. Frequently necrotic and degenerative changes supervene and bring about softening and disintegration. The dead tissue may then become firm and opaque from the deposition of lime salts, or it may become detached and leave behind a shallow excavation, to which the term atheromatous ulcer has been applied. Surrounding the necrotic focus there is always evidence of an acute inflammatory process, and doubtless the latter is the important factor in causing the cohesion of the valves which is sometimes observed. Valves the seat of chronic inflammation frequently become infected, in which case the vegetations characteristic of acute endocarditis appear.

Associated Conditions.—The stenosis or insufficiency of the valves resulting from chronic endocarditis necessarily throws an extra amount of work upon certain parts of the heart, the effect of which is to induce hypertrophy or dilatation, one or the other predominating according to the nature and gravity of the lesion and the state of the cardiac muscle. An enlargement which is just sufficient to accomplish the additional work is termed a compensatory hypertrophy. So long as the latter continues the patient experiences little or no discomfort, since the heart, notwithstanding the valvular lesion, is able to supply the arterial system with its normal quota of blood. When, however, the heart is unable to meet the increased requirements, dilatation ensues and compensation is said to be lost. Under these circumstances the veins become surcharged with blood and the arteries depleted, a condition which immediately calls forth a train of distressing symptoms.

Changes in the myocardium are rarely absent in chronic endocarditis; and, as a rule, more depends upon the character, extent, and location of these changes than upon the valvular defect itself. The lesions of the heart-muscle, which comprise hyperplasia of the connective tissue and various degenerations of the parenchyma, may be related in several ways to the valvular disease. In the first place, they often develop simultaneously with endocarditis as the result of one and the same cause. Again, they may be due to sclerosis of the coronary arteries which has developed at a later period than the endocarditis and from causes in no way related to the latter. Thus compensatory hypertrophy is often well maintained until old age itself effects sclerotic change in the arteries of the heart. In some cases the myocardial lesions, at least in part, are directly dependent upon the valvular affection. Thus in mitral disease Banti has found what he terms venous cirrhosis in contradistinction to arterial cirrhosis. The coronary veins and their branches are dilated, the intermuscular tissue is overgrown, and the

muscle-fibers are vacuolated, degenerated, and atrophied. This condition appears to be dependent upon imperfect emptying of the coronary vein into the right auricle. In aortic disease the valvular defect may seriously interfere with the filling of the coronary arteries, and in consequence there may be a secondary degeneration in the myocardium.

Disease of the Aortic Valve.—Disease of the aortic valve is conventionally divided into stenosis and insufficiency; but, as a matter of fact, these two conditions are often associated, the retraction and curling of the segments occasioned by sclerotic endocarditis giving rise to both incompetence and obstruction. Pure aortic stenosis is rare; it is usually due either to cohesion of the valve-segments or to constriction of the aortic ring. Aortic insufficiency may result from sclerotic endocarditis or actual rupture of one of the cusps. Rarely relative insufficiency may arise from the inability of normal valves to close an orifice which has been unduly distended by aneurysm of the ascending aorta or extreme dilatation of the left ventricle.

In aortic stenosis the increased resistance offered to the expulsion of blood from the left ventricle results in hypertrophy of that chamber; but, as there is little tendency to dilatation, the enlargement is rarely so extreme as in aortic regurgitation. Ultimately, however, the ventricles may yield to the severe strain, and, in so doing, occasion insufficiency of the mitral valves.

In aortic regurgitation the increased intraventricular pressure which follows the recoil of blood from the aorta in each diastole causes a permanent dilatation of the left ventricle, while the increased labor entailed by expelling an abnormal quantity of blood in each systole favors the development of a compensatory hypertrophy; as a consequence, the heart attains a larger bulk than in any other affection. Later sequences are stretching of the mitral ring, relative insufficiency of the mitral valve, enlargement of the left auricle, and finally dilatation of the right ventricle and relative insufficiency of the tricuspid valve.

Disease of the Mitral Valve.—In lesions of the mitral valve, as in those of the aortic valve, stenosis and insufficiency are frequently associated. Very often, however, one or the other condition predominates. Mitral stenosis is nearly always the result of a prenatal or a postnatal endocarditis. All degrees of obstruction are encountered. In severe cases fusion of the segments and constriction of the parts reduce the orifice to a narrow slit—the “buttonhole” form of mitral stenosis. More rarely the valve is converted into a smooth membranous cone, with its smaller aperture directed toward the apex of the heart—the “funnel-shaped” form of mitral stenosis. The changes in the heart resulting from mitral stenosis involve chiefly the left auricle and the right ventricle. On account of the hindrance to the outflow of blood, the left auricle first becomes dilated and then hypertrophied. In some cases the auricular walls attain a thickness of from $\frac{1}{8}$ to $\frac{1}{4}$ inch. The appendix of the auricle is especially affected; it may become enormously distended and elongated. Moxon records a case in which it measured $2\frac{3}{4}$ inches in length.

Thrombi are frequently found in the interior of the left auricle. They may be attached to the endocardium by slender pedicles so as to resemble polyps, or they may be entirely free and thus assume a globular shape. They may be so situated as to offer an additional impediment to the passage

of blood through the mitral orifice. Osler has reported a case in which sudden death resulted from the occlusion of a funnel-shaped mitral orifice by a ball-thrombus.

An increased tension in the pulmonary circulation, which is present throughout in mitral stenosis and which reaches its maximum when the auricular hypertrophy ceases to be compensatory, leads to hypertrophy and eventually to dilatation of the right ventricle. Marked dilatation of the right ventricle may finally render the tricuspid valve incompetent. The left ventricle is not enlarged, being usually normal in appearance; occasionally, however, it is unnaturally small.

Mitral regurgitation is the commonest form of valvular disease. It may be due to chronic endocarditis, resulting in curling and retraction of the mitral segments or in shortening and stiffening of the chordæ tendineæ. The most common cause is dilatation of the left ventricle or relaxation of its muscular walls, whereby the valve-segments are rendered incompetent to

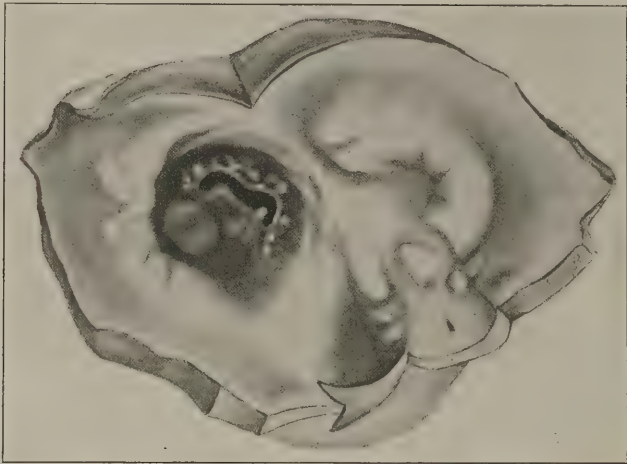


FIG. 171.—Buttonhole mitral valve (Ashton).

close the orifice during systole. Occasionally the disease results from rupture of the valve-curtains or the chordæ tendineæ.

The first effects of mitral regurgitation are enlargement of the left auricle and left ventricle. The former is due to the influx of blood from two sources, from the lungs and the left ventricle; the latter is due to the large amount of blood received from the auricle during diastole. As in mitral stenosis, the increased tension in the pulmonary circulation soon brings about hypertrophy and dilatation of the right ventricle, and eventually tricuspid insufficiency and dilatation of the right auricle may follow.

Disease of the Tricuspid Valve.—Tricuspid stenosis may be congenital or acquired. When congenital, it may be due to intra-uterine endocarditis or a vice of development; when acquired, the disease is always the result of endocarditis which is usually of rheumatic origin. In a series of 154 cases, comprising 114 collected by Leudet and 40 by Herrick,¹ 114 were

¹ *Boston Med. and Surg. Journ.*, March 18, 1897.

females, 32 were males, and in 8 the sex was not stated. In 84 of these cases the age was between twenty and forty years. In only 12 instances was the tricuspid valve alone involved. It is noteworthy that in 138 cases, or nearly 90 per cent., mitral stenosis coexisted. In 39 cases both the aortic and mitral valves were involved. In no case, however, as Ashton points out, were tricuspid and aortic stenosis combined, unless there existed also mitral stenosis. Tricuspid stenoses probably always brings about marked enlargement of the right auricle; but, as other valves are usually affected, it is common to find a general enlargement of the heart.

Tricuspid regurgitation is usually secondary to the lesions of the mitral valve or to diseases of the lung which obstruct the pulmonary circulation, such as emphysema, chronic bronchitis, and fibroid pneumonia. In these cases the valve-segments may remain normal, the insufficiency being relative and entirely dependent upon the dilatation of the right ventricle and the distention of the tricuspid orifice; or the valve-segments themselves may slowly undergo sclerotic and degenerative changes, as a result of the increased tension to which they are subjected. Occasionally the disease develops independently as the result of acute or chronic endocarditis. Tricuspid regurgitation affects the right side of the heart, as mitral regurgitation affects the left side. The right auricle and the right ventricle are usually considerably enlarged.

Disease of the Pulmonary Valve.—Stenosis of the pulmonary valve is almost invariably of congenital origin. It is often associated with other anomalies of development, such as a pervious state of the ductus arteriosus and defects in the cardiac septa. In rare instances the disease is acquired in the course of acute rheumatism or some other infection. Chevers and others have shown that pulmonary tuberculosis is an extremely common cause of death in subjects with congenital pulmonary stenosis.

Pulmonary insufficiency is the rarest form of valvular disease. Pitt states that only 17 cases have been noted in the postmortem room at Guy's Hospital, out of 11,000 examinations, during a period of twenty-three years. He has collected from various sources 99 cases, all of which were confirmed by necropsy. The affection may be congenital or acquired. The latter may result from infectious endocarditis or dilatation of the pulmonary artery. Occasionally a thoracic aneurysm, by pressing on the pulmonary artery near the valves, causes an adhesive inflammation which results in insufficiency.

THE ARTERIES.

Retrogressive Changes.—**Hypoplasia.**—In certain cases of chlorosis the walls of the large arteries are unnaturally thin and elastic and the lumen of the aorta is no larger than that of a child's. Some aneurysms seem to be dependent upon a defective development of the media. Hypoplasia of the blood-vessels has also been observed in hemophilia.

Atrophy of the arterial walls may occur as the result of wasting diseases. In atrophy of individual organs the blood-vessels may share in the process. As a rule, the loss of substance is intimately associated with changes of an inflammatory or degenerative character.

Fatty changes are common. They may be confined to the endothelial cells of the intima, but in some instances the deeper layers of the intima and the muscle-cells of the media are also affected. They occur in association

with other morbid changes in arteriosclerosis; as an independent affection they may result from the action of various toxic substances present in the blood. To the naked eye the affected areas are whitish and opaque; microscopically the cells are granular and filled with minute oil globules. Fatty changes of this kind may lead to rupture of the vessel, or they may be followed by calcareous infiltration.

Calcareous infiltration is generally met with as an accompaniment of fatty degeneration or arteriosclerosis. The intima and the media are the parts affected. In extensive calcification of the media the artery may appear as a rigid tube.

Amyloid degeneration of the organs is first manifest in the arteries. In small vessels the degeneration affects all the coats; in large vessels the intima is chiefly involved.

Hyaline degeneration is frequently observed in the blood-vessels of old persons; it is an important factor in arteriosclerosis; it often attacks the arterioles and capillaries in infective processes and intoxications; and finally it is often well marked in the arteries of certain sarcomas (cylindromas). Small vessels may present a beaded appearance from the irregular deposit beneath the endothelium of a clear, homogeneous, refractive substance, which reacts well with Weigert's fibrin-stain. In the large vessels the walls are more uniformly affected; the process, however, is most marked in the intima and connective tissue of the media.

Hypertrophy.—Hypertrophy of the arteries results from increased blood-pressure, and is seen in the establishment of a collateral circulation when an important arterial trunk has been occluded.

Inflammations.—Acute Arteritis.—Acute inflammation of the arteries may result from external injury, extension of disease from adjacent structures, or from certain general infections or intoxications. Recent bacteriologic investigations have thrown much light upon the pathology of acute arteritis occurring in the course of infective processes. Boinet and Romary were able to excite acute arteritis by injecting into the circulation various pathogenic bacteria, without having previously injured the intima. They further demonstrated that the bacteria themselves were not necessarily the cause of the inflammation, since the latter could be excited by the injection of bacterial toxins alone. It is conceivable that the noxious agent may reach the intima through one of three channels—the main blood-stream, the vasa vasorum, or the lymphatics. Careful bacteriologic and histologic studies indicate, however, that in most instances the irritant is carried directly to the intima by the blood in the main stream.

The macroscopic appearances vary considerably according to the cause of the inflammation. The intima is usually somewhat reddened by liberated blood-pigment. More or less circumscribed, slightly elevated gelatinous plaques are frequently found projecting from the surface into the lumen of the vessel. More rarely thrombotic excrescences are observed, similar in all respects to the vegetations appearing on the valves of the heart in acute endocarditis.

Sometimes, but not so often as in phlebitis, the vessel is occluded at the seat of the lesion by an infective thrombus. To this group of cases the term *thrombo-arteritis* has been applied. Various opinions have been held as to the relation existing between the thrombus and the arteritis. Hunter taught that the inflammatory changes in the vessels were primarily effected, and

that the formation of the thrombus was a secondary event. On the other hand, Virchow and his followers have contended that the arteritis, instead of being the cause, is nearly always the result of the infective thrombus. Bacteriologic studies, however, do not support Virchow's contention, but indicate that in the majority of cases of infective arteritis the thrombosis is a secondary process. It has not been proved that the usual order of events may not be reversed in some instances, as is the case in that form of arteritis occurring in pyemia, in which the lodgement of a septic embolus is undoubtedly the primary factor.

Microscopically all the coats are involved, but not to the same extent. The intima and media sustain the brunt of the attack; and one of these tunics is affected more or less than the other, according as the invasion has started from without or from within the vessel. Nuclear fragmentation and necrosis are more or less marked in the intima. Beneath the endothelium there is an accumulation of spindle-cells or stellate cells, which are probably derived from the fixed connective-tissue cells or from the endothelial cells. The vasa vasorum are congested and surrounded by dense aggregations of small round cells.

Slight attacks of acute arteritis, no doubt, frequently end in complete resolution. That the lesions excited by acute infective processes may in some instances ultimately lead to arteriosclerosis is not improbable.

Acute aneurysmal dilatation or actual rupture of the artery sometimes occurs, when the process is localized and intense. Thrombo-arteritis not infrequently terminates in organization of the thrombus. When this occurs the fibrinous plug is gradually absorbed and replaced by a new formation of connective tissue, which springs from the coats of the artery. The ultimate result of this metamorphosis may be partial obliteration of the lumen of the vessel by fibrous bands or the complete conversion of the vessel into an impervious fibrous cord (*proliferative arteritis* or *endarteritis obliterans*).

Acute Suppurative Arteritis.—Acute suppurative arteritis may result from the extension of a septic inflammatory process from the neighboring tissues to the vessel-walls, or from the presence in the vessel of an embolus or thrombus containing pyogenic organisms. The microscopic changes consist in extensive necrosis of the tissues at the seat of the invasion and an abundant infiltration with round cells, the lesions being more marked in the adventitia or in the intima, according as the process extended from without or from within the vessel. In large arteries yellowish-white accumulations of pus may be visible to the unaided eye. Acute aneurysmal dilatation or rupture of the vessel is a possible result of the disease.

Arteriosclerosis.—(Atheroma; arteriocapillary fibrosis; chronic end-arteritis; arteritis deformans).

Definition.—A circumscribed or diffuse thickening of the arterial walls, especially of the intima, secondary to certain inflammatory or degenerative changes in the media.

The term arteriocapillary fibrosis, introduced by Gull and Sutton, is sometimes employed to designate the process when it involves the capillaries as well as the arteries. Thoma has suggested the name angiosclerosis for the condition when it affects the whole vascular system. When the disease affects the aorta and the large arteries and the degenerative changes are marked, it is by some spoken of as atheroma.

Etiology.—While arteriosclerosis sometimes occurs in persons quite

young, it is chiefly met with in later life; indeed, in many instances it is to be regarded as a natural accompaniment of senescence.

The causes which favor the early development of the disease operate through the blood, either by increasing its distensive force or by effecting changes in its composition. That mechanic strain itself is an important etiologic factor is confirmed by the fact that blood-vessels and parts of blood-vessels that are most subjected to the insults of the blood-stream are the earliest and most severely affected, and also by the fact that disease develops so frequently and so soon in persons who are engaged in occupations that require continued muscular exertion. Infections and intoxications which load the blood with noxious materials are common causes of arterial sclerosis; thus, syphilis, gout, rheumatism, Bright's disease, alcoholism, and chronic lead poisoning frequently excite it. In these cases the morbid agent may act in two ways: first, directly, by attacking the vessel-walls through the



FIG. 172.—Normal left carotid artery in cross-section: *a*, elastica interna; *b*, media; *c*, elastica externa; *d*, adventitia; *e*, vasa vasorum. Staining of the elastic fibers by Weigert's method (Malkoff).

vasa vasorum; and secondly, indirectly, by increasing the peripheral resistance, and in consequence raising the arterial pressure. It is highly probable that acute infectious diseases often produce, as in the case of chronic interstitial myocarditis, changes in the arteries which become the foundation of subsequent fibrosis. Pale-red gelatinous plaques have frequently been observed on the inner surface of the aorta after death from such diseases as erysipelas, acute rheumatism, and diphtheria. Hollis has cited the case of a child dead four days after an extensive burn, in whose aorta there were found streaks of early and evidently recent sclerotic changes. Microscopic study of the smaller arteries after infectious processes has revealed swelling and fragmentation of the endothelial cells, hyaline degeneration of the muscularis, and an accumulation of leukocytes in and about the vasa vasorum and in the perivascular lymph-spaces, lesions which seem quite capable of leading up to chronic endarteritis.

Morbid Anatomy.—Certain arteries show a special predisposition to sclerosis; thus, the aorta is most frequently, and usually most extensively, diseased. After the aorta, the vessels most commonly affected are the splenic, iliac, femoral, anterior tibial, coronary, cerebral, and brachial. On the other hand, sclerotic changes are rarely observed in the gastric, mesenteric, and hepatic arteries.

Two varieties of arteriosclerosis may be recognized: the circumscribed or nodular, and the diffuse.

Circumscribed or Nodular Form.—The macroscopic appearances vary according to the stage of the process. When the disease is of recent origin, an examination of the inner surface of the aorta reveals the presence of irregular plaques, having a translucent and somewhat gelatinous appearance. At a later period, these are firm and almost cartilaginous. When old, they are whitish or yellowish in color, and opaque from calcification and degeneration of their deeper layers. Extreme calcification leads to the formation of hard, brittle plates, which project into the lumen of the vessel and favor the deposition of fibrin. Not infrequently the necrotic tissue disintegrates and is converted into a soft, fatty detritus, which bursts through the superficial layers of the intima into the lumen of the vessel, thereby creating a so-called atheromatous ulcer. In many instances every stage of the process is represented within a limited area of the vessel; thus, fibrous nodules, calcareous plates, and atheromatous ulcers may be found side by side.

A microscopic examination of a sclerotic nodule shows that all three coats of the artery are more or less affected. The changes in the intima, in the first instance, consist in a marked proliferation of the subendothelial connective tissue. The endothelial lining itself, though pushed forward into the lumen of the vessel, often remains intact until the process is far advanced. The fusiform or stellate connective-tissue cells constituting the hyperplasia are at first well defined; but eventually the deeper ones, as the result of retrograde changes, chiefly hyaline and fatty degeneration, undergo disintegration and are replaced by oil-drops, crystals of cholesterin, fatty acids, and molecular debris. As an evidence of reaction, a round-cell infiltration is often observed in the vicinity of the necrotic areas. The media shows a distinct loss of tissue at points corresponding to the hyperplasia in the intima. The remaining muscle-fibers are the seat of hyaline and fatty degeneration; the elastic fibers are sometimes torn, and a round-cell infiltration is often present about the vasa vasorum. The adventitia generally shows a hyperplasia of the fibrous elements and a cellular infiltration.

Important changes take place in the *elastic tissue*. These are both degenerative and proliferative. The degenerative change begins early, usually in the inner layer of the media—the elastic lamellæ become thinner, their affinity for certain stains becomes altered, and finally they break down. The new formation of fibers is especially marked in the intima. The new elastic tissue is less resistant than the old, and yields readily to softening processes. Fig. 172 represents a normal artery stained to show the elastic fibers. In Fig. 173 the effect of the atheromatous process on the intima and media, including the elastic fibers, is well shown.

The Diffuse Form.—In this form of arteriosclerosis the process is more uniform, and often involves, in addition to the aorta and its branches, the smaller arteries, especially those of the kidney, brain, and heart. This form is usually observed in middle-aged men, and is very common in the negro

race. It is often associated with the nodular form in the large arteries. The intima is usually smooth; but, beneath the endothelial lining, white opaque patches are, as a rule, easily recognized. Microscopically the changes are similar to those observed in the nodular form. In the intima there is a marked hyperplasia of the subendothelial connective tissue; the latter, however, from having undergone hyaline degeneration, may appear almost structureless. In the smallest arteries the elastic lamina is often entirely wanting or represented only by a few disjointed fragments. The muscular fibers in the media are atrophied and the seat of fatty degeneration. In many of the arterioles, especially those of the kidney, all semblance to the normal structures is lost, the coats of the vessel being converted into a homogeneous hyaline tissue.

Pathogenesis.—In regard to the manner in which the changes peculiar to sclerosis are effected in the arterial walls, there has been considerable discussion. The idea originally entertained was that the lesions in the intima were primary and were the result of an inflammatory process excited by the direct action of an irritant conveyed to the part by the blood. At the present

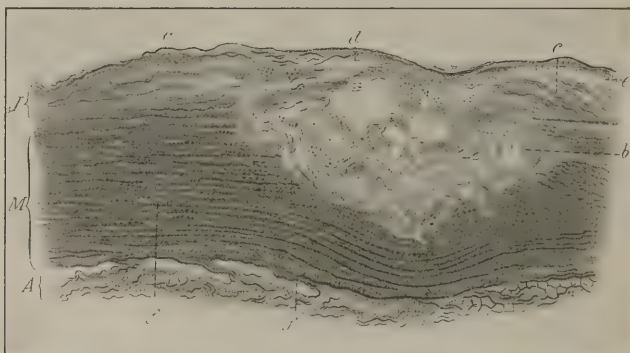


FIG. 173.—An atheromatous patch in the abdominal aorta which has not yet broken through: *J*, intima; *M*, media; *A*, adventitia; *b*, atheromatous necrotic focus in the intima and media; *c*, elastic fibers of the intima; *d*, elastic fibers which have persisted between the necrotic focus and the endothelial layer; *e*, thickened endothelium; *f*, infiltration of the media with small cells (Dmitrieff).

time this view has few supporters; most authorities now agree with Rokitsansky and Thoma in regarding the thickening of the intima as secondary to and dependent upon the degenerative changes in the media. According to Thoma, the thickening of the arterial walls, especially of the intima, is compensatory and designed to offset, in a measure, the loss of tissue sustained by the media.

To support this view and to prove that the sclerotic nodules, found post-mortem in the large arteries, simply fill up, during life, depressions produced by the weakening of the media, Thoma showed that casts made by forcing paraffin into the aorta and large arteries, under a pressure equal to that normally exerted by the blood, came out quite smooth and did not present the indentation which they would have shown had not the overgrowth of tissue in the intima closely corresponded to the loss of substance in the media.

While it is generally conceded that the thickening of the arterial coats is the result of the weakening of the media, the immediate cause of the

latter is a matter in which opinion is still divided. Köster believes that the primary lesion is an infiltration of the media; that is, a mesarteritis, and that the conversion of the cellular infiltration into fibrous tissue causes constriction of the vasa vasorum and thus induces secondary nutritive changes. According to Mott, degeneration of the media is often primarily due to obliteration or obstruction of the vasa vasorum and consequent defective nutrition of the muscular fibers. The causes of arteriosclerosis are so various that it is not unreasonable to suppose that the manner of its development may vary in different cases. It is not unlikely that the arteriosclerosis following certain infectious processes may originate in a mesarteritis or periarteritis, while that due to old age may result directly from a loss of elasticity in the media. High arterial tension may act also by first impairing the tonus of the muscularis, and thereby exciting a compensatory hyperplasia of the intima.

Tuberculous Arteritis.—Tuberculous arteritis may result from the direct extension of a tuberculous process originating outside of the vessel, from the presence within the vessel of an infected embolus, or from the

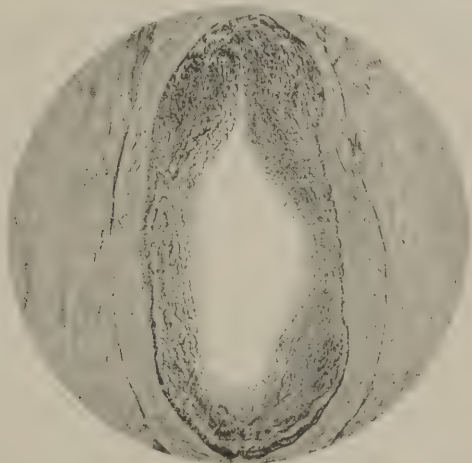


FIG. 174.—A branch of the coronary artery, showing syphilitic endarteritis. The new growth of the intima is almost entirely made up of elastic fibers which are in immediate relation with the thickened fenestrated membrane. Weigert's stain. $\times 50$ (Abramow).

direct implantation on the vessel-wall of bacilli contained in the blood. The disease most commonly affects the small arteries, especially those of the brain, lungs, and kidneys. The process is manifested by the presence of discrete tubercles in the adventitia or by thickening of the vessel-wall from a diffuse cellular infiltration. The latter consists of round cells, fusiform or stellate epithelioid cells, and a few giant cells. Partial or complete obliteration of the lumen of the vessel may result from marked infiltration and proliferation in the intima or from thrombosis. The new formation sometimes undergoes cheesy necrosis; and this, in the absence of thrombosis, may occasion aneurysmal dilatation or rupture of the vessel. In other instances the process culminates in a simple fibrous hyperplasia of the adventitia and intima, the lumen of the vessel being partially or completely occluded.

Tuberculosis of the large arteries is rare. Blumer¹ has reported 2 cases of tuberculous aortitis and has collected 8 others. In 7 of these the tubercle was probably due to direct implantation of infective material on the vessel-wall, and in 3 the tuberculous process originated outside of the vessel, either in consolidated lung or adherent lymph-gland.

Syphilitic Arteritis.—Syphilitic arteritis may result from the spread of a local syphilitic affection or from the direct action of the toxin upon the blood-vessel walls. The cerebral arteries, coronary arteries, and aorta are the vessels most frequently involved. While the lesions are often those of arteriosclerosis, there is a special form of syphilitic arteritis in which the chief feature is a marked hyperplasia of the adventitia and intima, which obliterates partially or completely the lumen of the vessel. This hyperplasia consists, according to its age, of epithelioid cells and round cells—in the really typical instances arranged to form gummas in the vessel-wall, especially the adventitia—or of fully developed fibrous tissue. In some cases all three coats are involved. When the process is arrested, an attempt at regeneration is apt to take place, with new formation of elastic fibers in the intima from the fenestrated membrane.

There is much less tendency to degeneration in syphilitic than in other forms of chronic arteritis. In the cerebral arteries the process sometimes assumes a nodular form, owing to cellular accumulations and gummatous formations in the adventitia.

Periarteritis Nodosa.—Periarteritis nodosa is a rare form of arterial disease characterized by the appearance, on the walls of the vessel, of multiple nodules varying in size from that of a millet seed to that of a pea. Microscopic examination of these nodules reveals marked cellular infiltration of all the coats of the artery and more or less extensive degenerative and necrotic changes. Thrombosis and acute aneurysmal dilatation frequently accompany the process. The cause of this disease is not apparent; but the sudden onset, acute course, and muscular atrophy suggest the operation of some infective agent. The vessels of the brain usually escape, the change being most marked in the peripheral arteries and in those of the heart, liver, spleen, mesentery, and kidneys. Periarteritis nodosa is interpreted by Eppinger as a form of congenital aneurysm, dependent upon defective development of the elastic coat and characterized by multiple aneurysmal dilatations in many of the medium-sized arteries; but there is no good evidence in favor of this view.

Aneurysm.—An aneurysm is a more or less circumscribed dilatation of an artery. When the dilatation involves the whole contour of the vessel, it is termed a *fusiform aneurysm*. When the bulging involves only one side of the vessel and communicates with the latter by a relatively small orifice, it is termed a *saccular aneurysm*. The term *cirroid aneurysm* has been applied to a form in which the vessel is not only dilated, but also tortuous and elongated. Rupture of the intima, with the passage of blood between the outer tunics of the vessel, constitutes a *dissecting aneurysm*. The blood may ultimately escape into the surrounding tissues, or it may return to the lumen of the vessel through another opening in the intima. A condition in which the blood has burst through all the coats of the vessel and has, out of the surrounding tissues, formed for itself an adventitious sac, is termed a *false aneurysm*. As varieties of the latter may be mentioned: (a) *Aneu-*

¹ *Am. Jour. Med. Sci.*, Jan., 1899.

rysmal varia, a condition in which both an artery and a vein have been wounded, and the blood from the former flows directly into the latter; and (b) *varicose aneurysm*, a condition in which an artery and a vein communicate indirectly through an intermediate adventitious sac.

Etiology.—In the vast majority of cases, aneurysm results from degenerative changes in the vessels, excited by syphilis, alcoholism, gout, lead poisoning, or immoderate physical exertion. In at least 50 per cent. of the cases, a history of syphilis is obtainable. Age, sex, and occupation are important factors. Of 173 cases of aortic aneurysm tabulated by Browne, 113 occurred between the ages of thirty-five and fifty-five years. These statistics coincide closely with those recorded by Crisp, who analyzed 551 cases and found 398 between the ages of thirty and fifty years. Between 80 and 90 per cent. of all cases occur in males. Persons engaged in occupations which require violent muscular exertion are more liable to aneurysm than those who follow more quiet pursuits.

In some instances the disease apparently depends upon a defective development of the arteries. This is probably the explanation of the multiple aneurysms which are occasionally encountered in early life or even at birth. Virchow and Dickinson have called attention to the association, in some cases, of aneurysm and arterial hypoplasia. In the smaller arteries, dilatation may follow an eroding process which has invaded the walls of the vessel from without. Multiple aneurysms from this cause are frequently found in the lungs in advanced phthisis. Embolism is another cause of aneurysm in the smaller arteries. The embolus may be infectious and excite inflammation and degeneration of the vessel-walls at the seat of the occlusion, or it may be a calcareous plate; in which case, the breaking of the walls may have its origin in mechanic injury. The occurrence of multiple aneurysms in malignant endocarditis as the result of an acute mycotic arteritis was pointed out by Osler.

In the horse, aneurysm of the mesenteric arteries is not infrequently due to the *Strongylus armatus*. The larvæ of these worms bore into the coats of the vessel and bring about necrotic processes which culminate in aneurysmal dilatation.

Seats.—The aorta is by far the most common seat of aneurysm. After the aorta, the arteries most frequently affected, in order of incidence, are the popliteal, femoral, carotid, subclavian, axillary, and innominate. Browne states that there were 631 cases of aneurysm treated in St. Bartholomew's Hospital between 1867 and 1897. In 468 of these the disease affected the aorta, in 80 the popliteal, in 21 the femoral, in 14 the subclavian, in 8 the innominate, in 8 the carotid, and in 6 the external iliac. In 332 cases exclusive of aortic aneurysms, analyzed by Agnew, 145 were popliteal, 88 femoral, 21 carotid, 15 axillary, 13 innominate, 12 brachial, 12 subclavian, 9 intra-orbital, 3 temporal, 3 gluteal, and 1 subscapular.

Morbid Anatomy.—Aneurysms vary considerably in size; some, like those met with in the brain, may be almost microscopic, while those affecting the aorta may reach the dimensions of a child's head. The most common varieties are the saccular and fusiform.

When the aneurysm is of recent formation, all three coats of the artery may be demonstrable; but, as the dilatation increases, the media gradually disappears and the intima and adventitia become more or less thickened from a fibrous hyperplasia. The outlines of the tumor are often quite irregular

from the presence of secondary bulgings at points where the coats are most seriously weakened. Patches showing extensive sclerotic and degenerative changes and calcareous infiltration are generally visible. Fibrinous deposits are usually found in the interior of the sac. As a rule, these are more abundant in saccular than in fusiform aneurysms. In rare cases they completely fill the cavity. The oldest layers of the clot are attached to the intima, are pale, dry, and often laminated; while the most recent layers are nearest to the blood-stream, and are dark in color and soft. Extreme distention of the sac eventually leads to thinning of the coats of the aneurysm and to rupture. Even such an event may not prove immediately fatal, since life may be preserved for a certain period by an adventitious sac which has been formed out of the surrounding tissues.

Aneurysm of the Thoracic Aorta.—Aneurysms of the thoracic aorta are almost invariably associated with arteriosclerosis. Not more than one-seventh of the cases occur in females (17 in 114 cases—Browne). The saccular form is most commonly observed. The size varies from that of a bean to that of a cocoanut. They are usually single, but now and then a half-dozen or more of different sizes are encountered along the course of the vessel.

Aneurysms of the Ascending Portion of the Arch.—This is the portion most frequently involved. The dilatation may arise immediately above the valves, but in a larger number of cases it starts from a point an inch or more from the heart. The innominate artery is rarely involved. In the vast majority of instances the aneurysm springs from the convex side of the aorta and projects to the right; only rarely does it arise from the concave side of the vessel and extend to the left. The structures most liable to be pressed upon are the superior vena cava, pulmonary artery, and left recurrent laryngeal nerve. In about one-third of the cases death results from rupture, the latter occurring most frequently into the pericardium or right pleural cavity.

Aneurysms of the Transverse Arch.—Aneurysms affecting this portion of the aorta usually arise from the right half and from the posterior surface. The innominate artery and ascending arch are but rarely involved. The tumor may extend directly backward, or at other times upward and toward the surface. The structures most apt to be compressed are the trachea, sternum, left bronchus, esophagus, and left recurrent laryngeal nerve. Death from asphyxia is of common occurrence.

Aneurysms of the Descending Portion of the Arch.—Aneurysms of this portion of the aorta most commonly extend to the left and backward, occupying a position in the left interseapular region, close to the spine. The dorsal vertebræ and the ribs are frequently eroded. Other structures liable to be compressed are the esophagus, left bronchus, and trachea. The majority of cases terminate by rupture, which usually takes place into the left pleura, left bronchus, or esophagus.

Aneurysms of the Descending Aorta.—Aneurysms of the descending aorta usually occur a few inches above the diaphragm. As they lie to the left of the lower dorsal vertebræ or immediately in front of them, these bones are often eroded. The larger number of cases terminate by rupture, the latter occurring most frequently into one of the pleural cavities, especially the left, or into the esophagus.

Results.—As aneurysms increase in size, they displace the neighboring

structures or else compress them, and thus set up certain inflammatory and necrotic changes. Some of these effects, however, are purely mechanic. Whether, unaided by other lesions, aneurysms can produce hypertrophy of the heart, is still an unsettled question; but the evidence, both clinical and pathologic, does not favor the affirmative view. In only 72 cases of the 173 tabulated by Browne was there any degree of hypertrophy; and in many of the cases in which the latter was observed, there were valvular lesions present to which the enlargement could be attributed. Aneurysms of the ascending arch occasionally distend the aortic ring to such an extent that aortic valves are rendered incompetent.

On account of the relation which the aorta holds to the trachea and bronchi, the lungs frequently suffer. Death from asphyxia is not uncommon, especially in aneurysms of the transverse arch. Fränkel, who has made a special study of the pulmonary complications of aortic aneurysms, has divided them into four groups: Exudative pneumonia, fibroid pneumonia, gangrene, and tuberculosis. All of these, he states, are dependent more or less upon mechanic causes; that is, the pressure upon the main bronchus. At the point of greatest pressure, necrotic ulceration occurs; and the excretion from this, flowing into the lungs, causes inflammation or coincident infection. Another complication, not alluded to by Fränkel, resulting from pressure upon a bronchus, is bronchiectasis. Compression of the pulmonary artery not infrequently gives rise to pulmonary edema or hydrothorax. Erosion of the sternum, vertebrae, and ribs occurs in many instances. Occasionally an aneurysm of the descending aorta lays open the spinal canal and involves the cord.

The most common termination of thoracic aneurysms is by rupture. The latter was the cause of death in 64 of the 150 cases tabulated by Browne. This accident occurs twice as often in aneurysms of the descending arch and descending aorta as in aneurysms of the ascending and transverse arches; which proves, according to Mir, that the more freely the aneurysm can develop, the more likely it is to rupture. As regards the point of rupture, of the 64 cases analyzed by Browne, the left pleural cavity was the seat in 20, the pericardium in 11, the right pleural sac in 8, left bronchus in 7, the esophagus in 7, the right lung in 3, and the pulmonary artery in 1. In 3 instances the rupture was external, and in 1 into the subpleural connective tissue on the right side. Of 32 cases of ruptured thoracic aneurysm analyzed by Kelynack, the pericardium was the seat in 13, the left pleura in 7, the esophagus in 3, the trachea in 2, the right pleura, the left lung, the right bronchus, and the superior vena cava in 1 each; in 3 the rupture was external. Of 50 cases studied by Ames and Townsend, in 27 rupture took place through all the coats at once, in 6 through the intima and media primarily and through the external tunic later, and in 8 there was a dissecting aneurysm. Rupture into adjacent blood-vessels is not very rare. Pepper and Griffith have collected 29 cases in which rupture took place into the superior vena cava.

Lamplough cites 16 cases in which aortic aneurysms communicated with the pulmonary artery. Very rarely rupture occurs into the heart, as in a case reported by McPhedran, in which the communication was with the left auricle.

In some instances aneurysms remain latent for an indefinite period.

Williams mentions a patient who had been suffering for thirty years with an aneurysm of the arch of the aorta. Occasionally spontaneous cure results from the complete obliteration of the sac by laminated clot.

Aneurysm of the Abdominal Aorta.—Aneurysms of the abdominal aorta are much less common than those of the thoracic aorta. Of 173 cases of aortic aneurysm collected by Browne from the postmortem records of St. Bartholomew's Hospital, in only 23 was the abdominal aorta involved. The usual seat of the lesion is immediately below the diaphragm, in the region of the celiac axis. It occurred in this position in 20 of the 23 cases noted above. The uniformity in the location of the aneurysm has been attributed to the constriction of the artery at each ventricular systole by the tendinous band which arches over it as it passes between the pillars of the diaphragm, and to the sudden reduction in the lumen of the vessel that is naturally found about an inch and a half below the diaphragm. Erosion of the upper lumbar vertebrae is observed in nearly half of the cases; and in some instances the caries is so extensive that membranes of the spinal cord are exposed.

Aneurysms of the ventral aorta usually terminate by rupture of the sac into the retroperitoneal space or into the general peritoneal cavity. More rarely rupture takes place into one of the pleural sacs, inferior vena cava, intestine, mediastinum, or pelvis of the kidney.

THE VEINS.

Phlebitis.—Acute inflammation of the veins may result from injury or the extension of inflammation from adjacent tissues, or it may be induced by morbid changes in the circulating blood. In the latter cases the disease may be excited directly by the implantation of bacteria from the blood, or indirectly by contact with a thrombus or an embolus. The process is manifested by cellular infiltration of the coats of the veins and a variable amount of necrotic change in the tissue-cells, the intima being more or less affected than the adventitia according as the disease originated as an endophlebitis or a periphlebitis. The lumen of the vessel is very often occluded by a thrombus (*thrombophlebitis*), and this clot may be the primary lesion; but recent bacteriologic studies indicate that in the majority of cases the thrombosis is secondary to the phlebitis. In suppurative thrombophlebitis the thrombus may soften and excite septic embolism. In other cases organization follows, and the lumen of the vein is partially or completely obstructed by cicatricial tissue (*phlebitis obliterans*). A vein-stone or phlebolith is occasionally formed by the calcification of a partially organized thrombus.

Chronic Phlebitis; Phleboscclerosis.—A chronic inflammatory process, characterized by fibrous hyperplasia and analogous to arteriosclerosis, is sometimes observed in the veins. It usually results from prolonged venous stasis or from some chronic intoxication. The most marked examples of the disease have been observed in connection with syphilis.

Varices or Dilated Veins (Phlebectases).—The development of varices is favored by causes which impede the venous circulation and by such morbid changes in the veins themselves as lessen the tonicity of their walls. The vessels most commonly affected are the spermatic, pudendal, hemorrhoidal, and saphena veins. Cirrhosis of the liver, by obstructing the portal

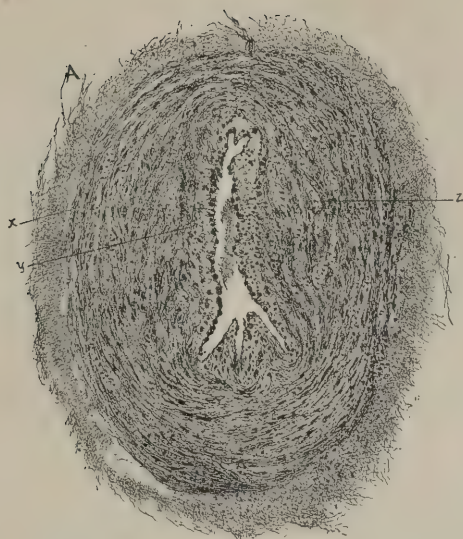


FIG. 175.—Section of vein almost closed by thickening of the muscularis. The thickened muscularis is only partly composed of true muscular tissue, which has been torn apart and thrown into wavy strands by morbid fibroid tissue which has grown in it. *z*, Line of separation of the fibrous coat from the muscularis; *y*, line of separation of the muscularis from the intima. All the tissue between *x* and *y* is muscularis; the thickening is very great. At *y* the separation of muscularis from intima is clearly marked, but at other parts of the circuit there is no distinguishable boundary line. The intima is much thickened, but not so much as the muscularis. The caliber is beaded with endothelial nuclei. $\times 56$ (Meigs).



FIG. 176.—Another section of the vein shown in Fig. 175, showing also great thickening of the walls, but of a different character. The opening is almost filled by irregular projections from the intima. One of these (*o*) is composed of the plicated membrane, which is curiously folded and knotted. There is another somewhat similar knot of smaller size and several irregularly shaped projections of the intima, which fill a large portion of the caliber. The muscularis is irregularly thickened. Parts of it are hard to recognize as involuntary muscle, being more like morbid fibroid tissue. *p* is distinctly muscular tissue; *m* shows the muscularis and intima shading together without a distinguishable line of separation; *n* marks a spot where the separation of the two coats is distinct. $\times 56$ (Meigs).

circulation, frequently occasions varices in the epigastric, mammary, esophageal, and hemorrhoidal veins. Chronic valvular disease, pregnancy, and pelvic tumors are common causes of phlebectases in the vessels of the legs. Local varicosities may be due to occlusion of a large venous trunk by an embolus or to pressure exerted in the vessel from without by a tumor. Atony of the walls of the veins, induced by defective circulation or constitutional disorders, also plays an important part in the development of the disease. At first the veins are simply uniformly dilated, but as the disease advances they become elongated and tortuous. Lateral sacculations are often developed, giving to the vein a knotty appearance. As a rule, the dilatation is accompanied by a thickening of the walls, the result of a fibrous hyperplasia; in some cases, however, the coats of the vessels are perceptibly thinned.

The most important sequences of varicose veins are edema, hemorrhage, thrombosis, and chronic inflammation or ulceration of the surrounding tissues.

THE LYMPHATIC VESSELS.

Lymphangitis.—Acute inflammation of the lymphatic vessels is never a primary disease, but always results from inflammation of surrounding tissues or of parts drained by the affected vessels. In the skin and subcutaneous tissue, acute lymphangitis may be recognized by interrupted red streaks running from the primary focus of infection to the nearest lymph-glands. The minute changes consist in swelling of the intima, proliferation and desquamation of the endothelial cells, and an infiltration of the walls, and often of the surrounding tissues (perilymphangitis), with round cells. Coagulation of the lymph, with the formation of a thrombus, is of frequent occurrence. Slight attacks often end in resolution. In severe septic cases the thrombus softens, the vessel ruptures, and the neighboring parts become infiltrated with pus. Occasionally the process ends in fibroid thickening of the coats of the vessel, with partial or complete obliteration of its lumen (chronic lymphangitis).

Lymphangiectasis.—Dilatation of the lymphatic vessels may be congenital or acquired. The congenital form, which is more of an overgrowth than a dilatation, occurs in the tongue (macroglossia), in the lip (macrocheilia), the labium, and in other subcutaneous parts. When the formation is more or less circumscribed, it is termed a *lymphangioma*.

Acquired lymphangiectasis results from complete occlusion of important lymphatic channels. Anastomotic communication between the lymphatics is so free in most parts of the body that large vessels, and even the thoracic duct, may be obstructed without serious consequences; only in exceptional cases is the impediment to the flow of lymph sufficient to cause stagnation and to lead to dilatation of the vessels. The obstruction may be due to thrombosis, inflammatory thickening, lodgement of filaria, or to compression of the lymphatic vessels by a tumor. Acquired lymphangiectasis is most commonly observed in the lower extremities and external genitals, where it is accompanied by an enormous hyperplasia of the skin and subcutaneous tissues, and constitutes the disease known as *elephantiasis*.

Tuberculosis.—The extension of tuberculosis from the primary focus of infection is usually effected through the lymphatic channels, and in some instances the vessels themselves are involved in transmitting the disease.

In tuberculous ulceration of the intestines, miliary tubercles are frequently found in the serous coat along the lymphatics which run to the nearest mesenteric glands. Tuberculous lesions of the skin and subcutaneous tissues are sometimes associated with tuberculous lymphangitis. The invasion of the thoracic duct by tubercles may lead to a general infection.

Syphilis and Glanders.—The lymphatic vessels may be involved in the course of syphilis and of glanders.

Tumors.—The two primary growths of the lymphatics are the *lymph-angioma*, to which reference has already been made, and the *endothelioma*; the latter is usually found in the pleura, membranes of the brain, peritoneum, or skin, and may owe its origin to a proliferation of the endothelial cells lining the lymphatic vessels. Cancerous infiltration of the lymphatics may occur in the extension of the disease by metastasis.

Obstruction of the Thoracic Duct.—This results from: (a) Pressure on the duct from without by tumors, enlarged lymph-glands, or aneurysms; (b) the growth of tumors in the walls of the duct; (c) inflammatory stricture; (d) the impaction of adult filaria; (e) thrombosis of the left innominate vein or of the duct itself; (f) the backward pressure of blood in the subclavian vein, occasioned by tricuspid insufficiency.

The results of obstruction to the main lymphatic trunk are variable. In many instances, especially when the obstruction is in the lower part of the duct, the establishment of a collateral circulation averts serious consequences. If for any reason the latter fails to compensate, then extensive lymphangiectasis may follow, or the chyle may escape either by transudation or by actual rupture of the thoracic duct. The free chyle may infiltrate the tissues or may collect in one of the serous sacs, constituting in the peritoneum chylous ascites, and in the pleural sac chylothorax.

THE LYMPHATIC GLANDS.

Retrogressive Changes.—Atrophy and Degeneration.—Atrophy of the lymphatic glands is characterized by a decrease in the number of lymphoid cells. It occurs in old age and in wasting diseases. The glands are small, and, on section, firm from a relative preponderance of fibrous tissue. In some cases fatty infiltration of the reticulum compensates, in a measure, for the loss of substance occasioned by the disappearance of some of the lymphoid elements.

Pigmentation.—Pigments of various kinds are intercepted by the lymph-glands, whither they are brought by the lymphatic vessels. Acute hemorrhagic extravasations, chronic malaria, and Addison's disease are common causes of pigmentation. In many instances the colored particles are extraneous substances introduced into the body from without; thus, the bronchial glands are often deeply discolored by coal-dust and other foreign matter inhaled with the air. The artificial pigments employed in tattooing are sometimes taken up by the carrier-cells and deposited in neighboring glands. The pigment-granules are found chiefly in lymph-sinuses, but ultimately they may appear also in the follicles and even in the trabeculae. Their presence frequently occasions an inflammatory reaction which culminates in a hyperplasia of the connective tissue, partial atrophy of the lymphoid elements, thickening of the capsule, and the formation of adhesions between the gland and adjacent structures.

Calcareous infiltration usually occurs in connection with tuberculous lymphadenitis and other processes which impair or destroy the vitality of the lymphoid tissue. It is occasionally observed, however, in healthy glands when the blood is surcharged with lime salts, as in osteomalacia and extensive caries.

Amyloid degeneration of the lymphatic glands is not uncommon in chronic suppuration. In rare instances the glands alone are affected; but, as a rule, they only share in the process when it is widespread. When the degeneration is sufficiently advanced the glands are enlarged, and, on section, are firm, gray, and translucent. Slight involvement can only be detected by microscopic examination or by the characteristic staining reactions. The walls of the blood-vessels and the trabeculae are the parts affected; the lymphoid cells, though seriously compressed by the amyloid material and even ultimately destroyed by it, rarely if ever share in the transformation.

Hyaline degeneration is sometimes associated with other changes of an inflammatory or degenerative character. It affects chiefly the walls of the blood-vessels and the fibrous tissue of the glands.

Inflammations.—**Acute lymphadenitis** is sometimes excited by the direct extension of an inflammatory process from a contiguous structure. In other cases the primary focus of inflammation is some distance from the affected gland, the irritant having reached the latter through the afferent lymphatic vessels. General infections, such as bubonic plague, diphtheria, scarlatina, and small-pox, are also common causes of lymphadenitis. In these cases the glands in the vicinity of the infection atrium are most seriously affected; but, as the bacteria or their toxins are often widely disseminated, the lymphoid nodes in other parts of the body rarely escape. The inflamed gland is swollen, injected, and soft. On section, the surface is smooth, reddish gray in color, and in severe cases studded with dull yellowish foci representing areas of necrosis.

Microscopically the normal structure is often unrecognizable. The blood-vessels are distended, and hemorrhagic extravasations are observed. The lymph-sinuses are filled with desquamated endothelial cells, red corpuscles, and leukocytes. Round-cell infiltration is apparent throughout the gland. Possibly some of the lymphoid cells proliferate; but many show evidences of a retrograde transformation, which is manifested in the swelling of their protoplasm and in the disintegration of their nuclei. The nuclear fragments are found free and also included within phagocytes, some of which are of enormous size (macrophages). When severe the process ultimately results in complete necrosis; in which case the cells are represented by homogeneous or finely granular areas which no longer possess staining affinities. The formation of fibrin in the coagulated material is sometimes suggested by indistinct fibrillation. When the necrosis is extensive, rupture of the gland may follow; in other cases the dead cells may be slowly absorbed and replaced by scar-tissue, or they may be retained, encapsulated, and subsequently calcified. When pyrogenetic organisms invade the gland the process may terminate in suppuration. Finally, when the irritation is not severe, but long-continued, the gland may become indurated from a hyperplasia of its connective-tissue elements.

Suppurative lymphadenitis is the result of pyogenic infection. It often occurs in glands whose afferent vessels communicate with infected wounds,

in the inguinal glands in gonorrhea, and in the cervical glands in diphtheria, scarlatina, and glanders. The inflamed gland softens, the septa break down, and the whole structure becomes permeated with pus. In many cases the capsule also gives way, and the purulent contents are discharged into the surrounding tissues, or externally if the gland is superficial. In other cases, before rupture takes place, a fibrinous perilymphadenitis reinforces the capsule, and under these circumstances the pus may become inspissated and perhaps ultimately calcified.

Chronic indurative lymphadenitis may be a sequel of acute lymphadenitis, or it may develop insidiously from the continued presence of foreign matters which have not been sufficiently irritating to excite acute inflammation. The affected gland is usually enlarged, and on section it is firm and



FIG. 177.—Tuberculosis and anthracosis of a lymphatic gland.

dense. The process consists in a hyperplasia of the fibrous tissue, involving the capsule, the trabeculae, and in some cases the intercellular reticulum. Occasionally the lymphoid cells share in the hyperplasia, but more frequently they suffer retrograde changes from the encroachment of the overgrown connective tissue.

Tuberculous Lymphadenitis.—Tubercle bacilli are conveyed to the lymph-glands through the lymphatics, or probably in rare instances through the blood-vessels. Characteristic lesions are sometimes present about the infection atrium in the skin or mucous membrane; but in many instances the tuberculous process appears to be primary in the glands, the tissues traversed by the bacilli escaping the infection. As a rule, the disease is more or less localized in certain groups of glands; but a generalized form

of tuberculous lymphadenitis is occasionally met with, in which most of the lymph-glands of the body are involved, other structures remaining comparatively healthy. The glands most commonly affected are the cervical, mesenteric, and bronchial. The cervical glands are most frequently infected through the tonsils, carious teeth, nose, or ear; and the mesenteric glands, through the intestinal wall. The bronchial glands are often involved secondarily in tuberculosis of the lungs acquired through the inhalation of infective material; but in some cases, beyond doubt, the pulmonary affection is not the cause, but the result, of a tuberculous lymphadenitis affecting the mediastinal and bronchial glands, which can be traced back to a primary lesion in either the cervical or mesenteric glands. The affected glands are enlarged. In the early stage, section reveals a grayish translucent material distributed uniformly throughout the gland or deposited in the form of discrete nodules. Later, caseation follows, and this material becomes yellowish white in color, opaque, and friable.

The process often terminates, especially in children, in softening of the caseous patches and rupture of the gland. At other times a reactive inflammation brings about an overgrowth of the connective-tissue elements of the gland and thickening of the capsule, and under these circumstances the necrotic tissue may in time become impregnated with lime salts.

Microscopically the chief features are the presence of epithelioid cells and giant cells surrounded by a round-cell infiltration. Bacilli are only visible in the early stages of the disease, and then they are found in and between the cells. In some cases, especially of cervical adenitis, the cellular proliferation is chiefly of the epithelioid type, round cells being comparatively few in number; under these circumstances, caseation is slow in appearing, and, as a result, the glands remain enlarged and indurated for an indefinite period. After necrotic changes have become well established, examination reveals granular or structureless areas wholly void of cellular elements and surrounded by zones of overgrown fibrous tissue in which pigment-granules are often present.

Syphilitic Lymphadenitis.—The lymph-glands in the neighborhood of the primary lesion are always swollen and indurated. In the secondary period a more or less generalized lymphadenitis is present; but there is nothing to distinguish it pathologically from other chronic forms of the disease. In the tertiary period the lymph-glands are occasionally the seat of a true gummatous formation. Amyloid degeneration of the lymph-glands is sometimes observed in connection with the inflammatory changes incident to syphilis; it affects chiefly the walls of the blood-vessels and the interstitial reticulum.

Tumors.—**Lymphadenoma; Lymphosarcoma.**—These terms are used to designate certain enlargements of the lymphatic glands dependent upon a hyperplasia of their lymphoid elements. The true character of these growths has not been determined. Although no micro-organism has been definitely associated with the affection, its resemblance to tuberculosis has suggested an infective origin. The glands most frequently involved are the cervical, axillary, inguinal, mediastinal, and retroperitoneal. In many instances growths of lymphoid tissue are also found in the various organs, especially in the spleen, liver, and kidneys. The affected glands vary in size from that of an almond to that of an egg; they may be either hard or soft. For a long time they remain isolated, freely movable, and unattached to the over-

lying tissue; but ultimately they become united to one another and to adjacent structures by inflammatory adhesions. Caseation and softening are rare, but not infrequently the lymphoid growth breaks through the capsule and infiltrates surrounding parts. On section, the glands are smooth, somewhat opaque, and of a grayish-white or reddish-gray color. When they are soft the cut surface yields, on scraping, a milky fluid not unlike that obtained from cancerous growths. Fibrous glands are firm and dry.

Microscopically the characteristic feature is a great increase in the number of lymphoid cells. The latter lie closely packed in the meshes of the reticulum and do not differ materially in appearance from the normal cells. In the early stages of the disease the structural relations are not altered to any great extent, and medulla, follicles, and septa are readily differentiated; later, in many cases, all histologic divisions are obliterated and the specimen

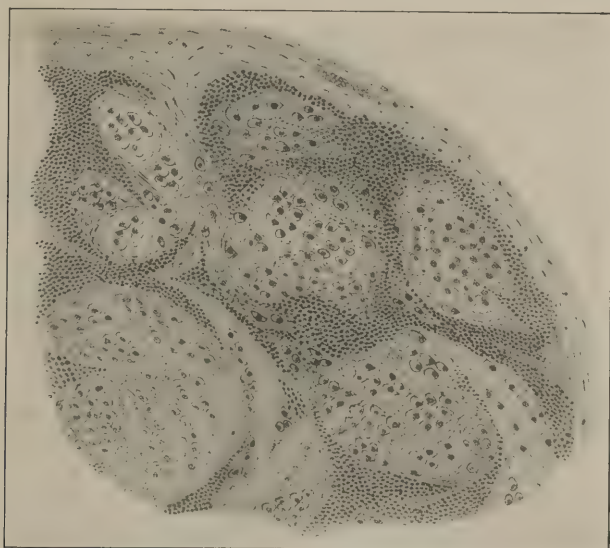


FIG. 178.—Carcinomatous infiltration of a lymph-gland.

presents a uniform aggregation of small round cells embedded in a fibrillar network. In some cases, however, the connective-tissue elements, instead of being reduced by encroachment of the lymphoid cells, undergo proliferation, thus rendering the gland firm and elastic.

Apart from the local disturbance excited by the glandular enlargements, changes in the composition of the blood sooner or later develop. The red cells fall off considerably in number, while the white cells remain approximately normal or are enormously increased. According as the oligocythemia is or is not accompanied by a leukocytosis, two forms of the disease have been recognized clinically, namely, leukemia and pseudoleukemia or Hodgkin's disease.

Le Count¹ has described a benign tumor resembling the lymph-glands in structure—a true lymphoma.

¹ *Jour. of Exper. Med.*, iv., 559, 1899.

Sarcoma.—This is the only primary growth of the lymphatic glands. Excluding the so-called lymphosarcoma, to which attention has already been directed, the principal forms are the round-cell, spindle-cell, and alveolar sarcoma. While several glands in the same group are often affected, there is very little tending, as in the lymphosarcoma or lymphadenoma, to involvement of neighboring glands; indeed, before the latter occurs, the tumor often breaks through the capsule and invades surrounding tissues, and even gives rise to secondary growths in distant organs. Sarcomas originate in the walls of the blood-vessels or in the connective-tissue reticulum. Secondary or metastatic growths are also encountered in the lymph-glands.

Carcinoma.—The lymphatic glands are the favorite seats of secondary cancer. Cells from the parent tumor are carried through the lymphatics to the nearest gland, where they multiply and are formed into nests by a fibrous stroma derived from the lymphadenoid tissue.

THE SPLEEN.

Congenital Anomalies and Displacements.—Complete absence of the spleen is rare. Hodenpyl, in reviewing the nine cases collected by him of apparent absence of the spleen, shows that only one can be accepted without question as an instance of this condition. In these cases the organ is usually represented by several small, scattered masses of splenic tissue (splenunculi), which, on account of their size and location, are in danger of being overlooked. More often, splenunculi are present in addition to the normal gland; they vary in number from three or four to a dozen or more, and are embedded in the peritoneal folds, omentum, the wall of the intestine, or, as in a case described by Biggs, in the tail of the pancreas. Abnormalities in shape, including marked lobulation, are sometimes observed. Rolleston describes a remarkable malformation in which the spleen gave off a long process extending down into the scrotum. In some instances the spleen occupies the right side of the abdomen, and the liver the left. According to Gruber, transposition of these organs occurred in 70 of 78 cases of dextrocardia.

Movable Spleen.—Movable spleen is seen most frequently in association with gastropptosis and enteroptosis, but it may occur as an independent affection. Relaxation of the ligaments from enlargement of the organ or from congenital weakness is the chief cause of the condition. A wandering spleen is usually found a little below its normal position, but in exceptional cases it may be as low as the pelvis. Sometimes the development of inflammatory adhesions serves to fix the spleen in its abnormal position. Twisting of the pedicle may cause, as in a case cited by Osler, hemorrhagic infarction and extensive necrosis.

Circulatory Disturbances.—Anemia.—This occurs as a part of general anemia, and is manifested by unusual pallor of the pulp.

Hyperemia.—*Active hyperemia* as a pathologic condition is most frequently seen in the specific fevers and septicemia. It is intimately associated with acute inflammation of the organ. *Passive hyperemia* occurs in the course of visceral diseases which impede the venous circulation, such as chronic valvular disease, emphysema, and cirrhosis of the liver. In the last affection, however, the enlargement of the spleen may be due in part, as Weber suggests, to a toxemia. The spleen is enlarged, firm, and of a

dark-red color. Section reveals distention of the veins, and often extensive pigmentation from the disintegration of red blood-cells. When long-continued, the organ becomes very hard and tough from hyperplasia of the fibrous tissue and secondary condensation and atrophy of the pulp (cyanotic induration).

Infarction of the Spleen.—The most common cause of splenic infarction is the plugging of a branch of the splenic artery by an embolus derived from the left heart or aorta. Thrombosis of the splenic artery, a condition occasionally met with in acute infective diseases, is a much less frequent cause of infarction. Thrombosis of the splenic vein, excited by inflammatory processes in contiguous organs or by extension of a thrombus from the portal vein, is a rare cause. Osler has recorded a case of splenic infarction induced by twisting of the pedicle of a movable spleen. The area of coagulative necrosis is generally wedge-shaped, with the base directed toward the surface of the organ; it projects somewhat beyond the surface of the surrounding tissue, and its consistence is more or less increased. The color of the infarct depends upon the variety: in the anemic form, which is the more common, it is dull white; in the hemorrhagic form, it is dark red from the extravasation of blood. The lesions may be single or multiple, and vary in size from that of a millet-seed to a bulk equal to more than one-half of the entire organ. Infarcts caused by noninfective emboli slowly disintegrate and are replaced by connective tissue, the site of the lesion being eventually marked by a whitish scar-like patch. Infarcts excited by infective emboli are speedily converted into abscesses. Thrombosis of the splenic vein or of its large branches results in total necrosis and hemorrhagic infiltration of the spleen.¹

Hemorrhage.—Traumatism and infarction are the most common causes of hemorrhage into the substance of the spleen. Small extravasations occur also in acute infective splenitis.

Retrogressive Changes.—Atrophy.—Simple atrophy occurs in old age and in wasting diseases. The organ is small, the capsule is wrinkled and opaque. On section, the substance is pale and the stroma conspicuous. Microscopic examination reveals atrophy of the Malpighian bodies and of the pulp, and an actual or relative increase in the fibrous trabeculæ.

Pigmentation.—The most marked hematogenous pigmentation of the spleen occurs in malarial cachexia, the granules being deposited in the trabeculæ, especially around the blood-vessels, and likewise in the lymphoid cells. Pigmentation is also one of the sequels of chronic venous congestion. In pernicious anemia and other severe cachexias associated with exaggerated hemolysis the condition is often well marked. Foreign substances, such as coal-dust, may reach the spleen through the blood and be deposited in the wall of the arteries.

Amyloid Degeneration.—Two forms are recognized: (1) The *sago* spleen, in which the capillaries of the Malpighian bodies are the parts chiefly affected; and (2) the *diffuse* form, in which the disease is more or less limited to the capillaries and veins of the pulp. The sago spleen is somewhat enlarged, its consistence is increased, and on section it is studded over with grayish translucent bodies varying in size from that of a pin's head to that of a millet-seed and closely resembling grains of sago. In the diffuse form of the disease, which is the less common, the organ is often

¹ Christomonas, *Ziegler's Beiträge*, xxiv., 519, 1899.

considerably enlarged; its structure is dense, and on section it presents a homogeneous, waxy, semitranslucent appearance. In this variety the Malpighian capsules usually escape, the disease beginning in the small vessels of the pulp, spreading to the trabeculæ, and finally, in rare instances, involving the pulp itself.

Hyaline degeneration is sometimes observed in the walls of the vessels and in the reticulum of the pulp.

Inflammations.—Acute Splenitis.—Acute nonsuppurative inflammation of the spleen frequently occurs in the course of infective diseases. The organ is enlarged, sometimes to three or four times its normal size, and the capsule is distended. On section, the tissue is at first firm and of a dark-red color; but as the process advances the pulp becomes soft and even diffuent, the color pales, and the Malpighian bodies appear abnormally prominent or are covered by the swollen pulp. Extensive hemorrhagic extravasations are not uncommon. Microscopic examination reveals an

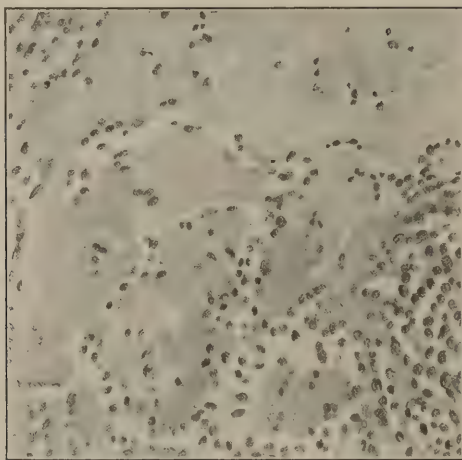


FIG. 179.—Amyloid degeneration of the spleen.

overdistention of the vessels, marked proliferation of the cells, both of the pulp and of the Malpighian bodies, and emigration of round cells. Degenerative changes appear early; these are shown in the fragmentation of the nuclei, the disintegration of the cells, the loss of affinity for nuclear stains, and in the presence of cellular detritus and pigment-granules, which are found free and enclosed within phagocytic cells. Acute splenitis usually terminates in resolution; but rupture of the organ, suppuration, and fibrous hyperplasia are possible sequels.

Purulent Splenitis.—Abscess of the spleen most frequently occurs in the course of some septic process, such as ulcerative endocarditis or general pyemia, the vehicle of infection being an embolus loaded with pyogenetic micro-organisms. It is rarely a sequel of the acute splenitis which accompanies typhoid and other specific fevers. Traumatism is an occasional cause. Inflammatory affections of adjacent organs may extend to the spleen and excite suppuration; in this way, gastric ulcer has given rise to abscess.

Embolic abscesses are usually multiple, and are situated near the periphery of the organ. Their formation is almost invariably preceded by infarction, the dead tissue being subsequently converted into a grumous reddish fluid. Occasionally splenic abscesses become encapsulated and subsequently transformed into caseous or calcareous nodules; but a much more frequent termination is perforation of the abdominal walls, or discharge of the pus into the peritoneum, stomach, colon, pleura, or lung.

Chronic Interstitial Splenitis.—Diffuse hyperplasia of the connective tissue may result from repeated attacks of acute splenitis, as in malaria, or from long-continued venous stasis, as in cirrhosis of the liver. General fibrosis is also observed in late syphilis and in rickets. Circumscribed areas of fibroid induration often mark the site of old infarcts. The spleen is enlarged and its consistence is increased. The capsule is usually thickened, and adhesions occasionally unite the organ to the adjacent structures. On section, the substance is firm, smooth, and often dark in color from the presence of free pigment. Microscopic examination reveals a great increase in the trabecular tissue and pigmentary infiltration of both pulp and connective-tissue cells.

Tuberculosis.—Acute miliary infection often occurs in general tuberculosis. The organ is studded, especially in the neighborhood of the capsule, with small gray tubercles, which may bear a close resemblance to the Malpighian bodies. Chronic tuberculosis is manifested by the presence of grayish-yellow caseous masses varying in size from that of a pea to that of a walnut. They may break down in the center and become semidiffuent; or, as in other organs, they may calcify. In the chronic form there is often extensive fibrous overgrowth.

Syphilis.—This disease may be manifested by gummatous growths or as a diffuse fibrous hyperplasia. Gummas are rare; Still was able to collect but 26 recorded cases; 20 of these were associated with acquired syphilis, and 6 with the hereditary form of the disease. The growths may be single or multiple, and vary in size from that of a pea to that of an egg. When the gumma is near the surface of the spleen the capsule is thickened, and adhesions often unite the organ to adjacent structures. Diffuse fibrous hyperplasia is of common occurrence in hereditary syphilis. The organ is large and tough, and its capsule is usually thickened. Amyloid degeneration is often seen in the acquired form, but it is rare in congenital syphilis.

Tumors; Cysts.—**Lymphadenoma** or **lymphosarcoma** is observed in leukemia and pseudoleukemia. The spleen is enlarged and usually firm; adhesions often unite it to the diaphragm and neighboring organs. The capsule may be thickened. The Malpighian bodies are enlarged into grayish-white opaque nodules, quite irregular in shape, and varying in size from that of a pea to that of a walnut. Infarcts are often present. Microscopic examination reveals great numbers of lymphoid cells, which are contained in the meshes of a fibrous reticulum. The trabeculae also are increased in size. Large nodules compress the surrounding pulp and bring about degeneration and pigmentation of the cells.

Carcinoma and **sarcoma** of the spleen are rare. The former is probably always secondary; the latter has been observed as a primary growth, but in the large majority of cases it is secondary.

Fibromas and **lymphangiomas** have been described.

A unique instance of **cavernous angioma** has been recorded by Langhans.

Cysts.—The small serous cysts occasionally found near the surface of the spleen are possibly due to dilatation of the lymphatic vessels or to the inclusion of small portions of peritoneal endothelium.

Extravasation-cysts are the result of traumatism.

Animal Parasites.—*Echinococcus*, *cysticercus*, and *Pentastomum denticulatum* occur.

Of 1771 cases of hydatid disease collected by Sommer, the spleen was affected in 42.

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